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(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ALLEN, David, George [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). ELDRED, Colin, David [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JUDKINS, Brian, David [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). MITCHELL, William, Leonard [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). SCOPES, David, Ian, Carter [GB/GB]; Oxford Glycosciences (UK) Limited, Abingdon Science Park, 10 Quadrant, Abingdon, Oxon OX14 3YS (GB).

(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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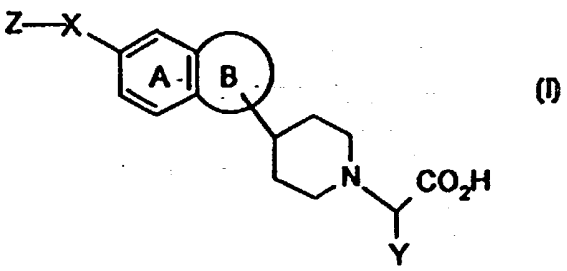
(54) Title: PIPERIDINE ACETIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT OF THROMBOTIC DISORDERS

(57) Abstract

The invention relates to compounds of formula (I) or a salt, solvate, or physiologically functional derivative thereof, in which: X is CH_2-CH_2, CH=CH, or C≡C; Y is hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, aryl, hetaryl, arylC_{1-4}alkyl, or hetarylC_{1-4}alkyl, wherein the aryl and hetaryl groups are optionally substituted by halo, nitro, C_{1-6} alkyl, C_{1-6}haloalkyl, hydroxy, C_{1-6} alkoxy, cyano, $-C(O)_nR^1$, $-NR^1S(O)_nR^2$, $-C(O)NR^1R^2$, or $-NR^1R^2$, wherein R^1 and R^2 are independently selected from hydrogen, C_{1-4} alkyl and C_{1-4} haloalkyl, and n is 0, 1, or 2; Z is piperidinyl, piperazinyl, or quinuclidinyl; ring B is a 5- or 6-membered aromatic heterocycle fused to ring A and is optionally substituted by a group -L-R wherein: L is a bond, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $S(O)_n$, $C(O)_n$, or $CONR^3$, wherein n is 0, 1, or 2, and R^3 is selected from hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl; and R is C_{1-6} alkyl, C_{4-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkoxy, cyano, $-NR^4R^5$, aryl or hetaryl, wherein R^4 and R^5 are independently selected from hydrogen, C_{1-6} alkyl and C_{1-6} haloalkyl, or together with the nitrogen to which they are bonded form a piperidinyl, morpholino, or pyrolidinyl group, and the aryl and hetaryl groups are optionally substituted by halo, nitro, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, cyano, $-C(O)NR^6R^7$ or $-NR^6R^7$ wherein R^6 and R^7 are as defined for R^4 and R^5 above, to processes for their preparation, to pharmaceutical compositions containing such compounds and to their use in medicine, particularly in the treatment of thrombotic disorders.



(I)

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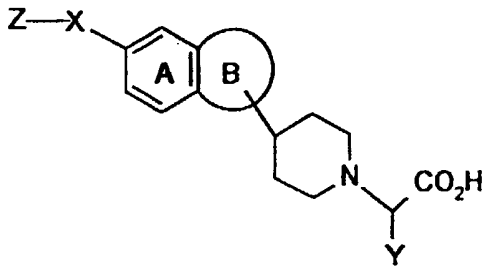
PIPERIDINE ACETIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT OF THROMBOTIC DISORDERS

This invention relates to heterocylic compounds, to processes for their preparation, to pharmaceutical compositions containing such compounds and to their use in medicine.

It is widely accepted that the glycoprotein complex Gp IIb/IIIa is the fibrinogen binding site on platelets that mediates the adhesive function required for platelet aggregation and thrombus formation. We have now found a group of non-peptidic compounds which inhibit fibrinogen-dependent platelet aggregation by blocking the binding of fibrinogen to the putative fibrinogen receptor Gp IIb/IIIa complex.

The invention thus provides a compound of formula (I)



(I)

or a salt, solvate, or physiologically functional derivative thereof, in which:

X is CH_2-CH_2 , CH=CH, or C≡C;

Y is hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, aryl, hetaryl, arylC_{1-4}alkyl, or hetarylC_{1-4}alkyl, wherein

the aryl and hetaryl groups are optionally substituted by halo, nitro, C_{1-6} alkyl, C_{1-6}haloalkyl, hydroxy, C_{1-6} alkoxy, cyano, $-C(O)_nR^1$. $-NR^1S(O)_nR^2$, $-C(O)NR^1R^2$, or $-NR^1R^2$, wherein

R^1 and R^2 are independently selected from hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, and n is 1, or 2;

Z is piperidinyl, piperazinyl, or quinuclidinyl;

ring B is a 5- or 6- membered aromatic heterocycle fused to ring A and is optionally substituted by a group -L-R° wherein:

L is a bond, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $S(O)_n$, $C(O)_n$, or $CONR^3$, wherein

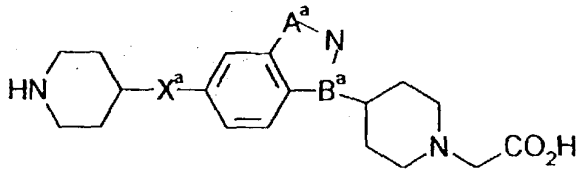
n is 1, or 2, and R^3 is selected from hydrogen, C_{1-4}alkyl, and C_{1-4}haloalkyl; and

R° is hydrogen, C_{1-6} alkyl, C_{4-7}cycloalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkoxy, cyano,
$-NR^4R^5$, aryl or hetaryl, wherein

R^4 and R^5 are independently selected from hydrogen, C_{1-6} alkyl and C_{1-6} haloalkyl, or together with the nitrogen to which they are bonded form a piperidinyl, morpholino, or pyrolidinyl group, and

the aryl and hetaryl groups are optionally substituted by one or more halo, nitro, C_{1-4} alkyl, hydroxy, C_{1-6} alkoxy, cyano, $-C(O)NR^6R^7$ or $-NR^6R^7$ wherein R^6 and R^7 are as defined for R^4 and R^5 above,

with the proviso that the disclosures of copending applications WO96/20192 and WO96/41803 are excluded from the scope of the present invention. Thus, the present invention provides a compound of formula (I) as defined above provided the compound is not of formula (a)



(a)

or a pharmaceutically acceptable derivative thereof, in which:

X^a is either CH_2-CH_2 or CH=CH; and

either A^a is $-\overset{\overset{Y^a}{|}}{N}-$ and B^a is –C=,
or A^a is –CH= and B^a is –N–, wherein
Y^a is hydrogen or phenylmethyl wherein the phenyl group is optionally substituted by one or more halogen atoms (where halogen represents fluorine, chlorine, bromine or iodine).

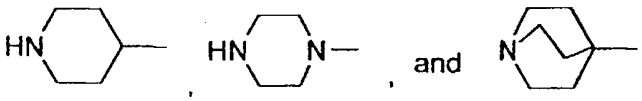
According to formula (I), ring B is suitably a 5- or 6- membered aromatic ring, fused to ring A, having 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulphur. Suitably the ring system A-B is an indazole, benzisoxazole, indole, benzisothiazole, benzofuran, benzothiophene, benzimidazole, or benzotriazole, and is preferably an indazole or benzisoxazole.

Ring B is preferably unsubstituted, or is substituted by a group $-S(O)_nC_{1-6}$alkyl or $-C(O)_nNR^4R^5$, suitably, $-SO_2CH_3$ or $-CONH_2$.

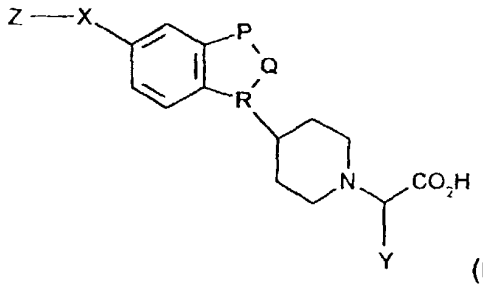
X is preferably CH_2-CH_2 or CH=CH. When X is CH=CH, it is preferably in the (E) configuration.

Y is preferably hydrogen or phenyl substituted by halo. Most preferably, Y is hydrogen.

Z is preferably selected from



According to a further preferred aspect, the invention provides a compound of formula (I) as represented by formula (Ia)



(Ia)

or a salt, solvate, or physiologically functional derivative thereof, in which:

P-Q-R is $N(R^8)$-N=C, $C(R^9)$=N-N, or O-N=C wherein:

R^8 is hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, $-R^{10}$, $-SO_2-R^{10}$, $-(C_{1-4}$ alkyl$)R^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, wherein

R^{10} is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{4-7} cycloalkyl, phenyl, or hetaryl, wherein

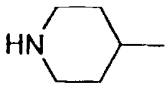
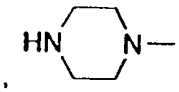
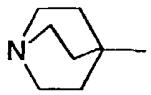
the phenyl and hetaryl groups are optionally substituted by halo, nitro, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, cyano, $-C(O)NR^{12}R^{13}$, or $-NR^{12}R^{13}$, wherein

R^{11}, R^{12} and R^{13} are independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl, or when R^8 is $-C(O)NR^{10}R^{11}$, R^{10} and R^{11} together with the nitrogen to which they are attached, form a piperidinyl or pyrolidinyl group;

R^9 is independently selected from groups listed in the definition of R^8 or is C_{1-10} alkoxy, C_{1-10} haloalkoxy, cyano, or, $-(C_{0-4}$ alkylene$)NR^{14}R^{15}$ wherein R^{14} and R^{15} are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or together with the nitrogen to which they are attached, form a piperidinyl, morpholino, or pyrolidinyl group;

X is CH_2-CH_2 or CH=CH;

Z is selected from


, 
, and 
; and

Y is hydrogen or phenyl optionally substituted by halo.

Of these, compounds wherein

(a) P-Q-R is $N(R^8)$-N=C;

(b) P-Q-R is $C(R^9)$=N-N; and

(c) P-Q-R is O-N=C

form separate embodiments of the present invention.

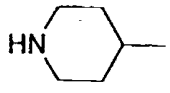
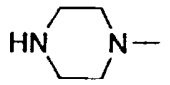
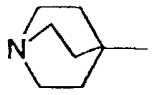
Preferred compounds of formula (I) include those wherein:

P-Q-R is $N(R^8)$-N=C, $C(R^9)$=N-N, or O-N=C wherein:

R^8 is hydrogen, or $-SO_2CH_3$ and R^9 is hydrogen or $-CONH_2$;

X is CH_2-CH_2 or CH=CH;

Z is selected from:


, 
, and 
;

Y is hydrogen or phenyl optionally substituted by halo:

and salts, solvates, and physiologically functional derivatives thereof.

Suitable compounds of formula (I) may be selected from:

{4-[1-(4-carbamoyl-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;

{4-[1-(4-carbamoyl-benzyl)-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;

{4-[1-(4-fluoro-benzenesulfonyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]piperidin-1-yl}-acetic acid;

(4-{1-[2-(4-fluoro-phenyl)-ethyl]-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid;

[4-[1-(4-nitro-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl]acetic acid;

{4-[1-cyclopentylmethyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-methyl-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-pentyloxy-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-bromo-benzoyl-carbonyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-dimethylamino-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-hydroxy-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-cyano-phenyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(3,4-dichloro-phenylcarbamoyl)-6-(2-piperidin-4-yl)-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[6-(2-piperidin-4-yl-(E)-vinyl)-1-(2,2,2-trifluoro-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-methylcarbamoyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-carbamoyl-benzyl)-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[6-(2-piperidin-4-yl-(Z)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-pentyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
(4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid;
(4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid;
4-[6-[2(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(4-fluoro-benzyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
(4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(4-tert-butyl-benzenesulfonyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid;
{4-[6-(2-piperazin-1-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-fluoro-benzyl)-6-(2-piperazin-1-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;

(4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid;
{4-[6-(2-piperidin-4-yl-(E)-vinyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[6-(2-piperidin-4-yl-ethyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[6-(2-piperazin-1-yl-ethyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl-acetic acid;
[4-[3-methoxy-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-methoxy-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-(E)-vinyl)-3-pyrazol-1-yl-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-(E)-vinyl)-3-pyrrolidin-1-yl-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-Morpholin-4-yl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-(E)-vinyl)-3-(pyrrolidine-1-carbonyl)-indazol-1-yl]piperidin-1-yl}acetic acid;
(4-[5-(2-piperidin-4-yl-ethyl)-3-(pyrrolidine-1-carbonyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid ;
{4-[3-isopropylcarbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-isopropylcarbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-cyano-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-morpholin-4-ylmethyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
(4-{5-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-indazol-1-yl}piperidin-1-yl)-acetic acid;
and salts, solvates, and physiologically functional derivatives thereof.

Particular compounds of formula (I) may be selected from:
{4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid;

{4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid ;
and salts, solvates, and physiologically functional derivatives thereof.

Further particular particular compounds of formula (I) may be selected from:
{4-[3-carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
and salts, solvates, and physiologically functional derivatives thereof.

Yet further particular compounds of formula (I) may be selected from:
{4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
and salts, solvates, and physiologically functional derivatives thereof.

According to a further aspect, there is provided a compound of formula (I) as defined above, provided that it is not a compound selected from:

(a) {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid, {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(Z)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid, {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid ; and/or

(b) {4-[3-carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid, {4-[3-carbamoyl-5-(2-piperidin-4-yl-(Z)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid, {4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid; and/or

(c) {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid, {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(Z)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid, {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;

or a salt, solvate or physiologically functional derivative thereof.

By the term "physiologically functional derivatives" is meant chemical derivatives of compounds of formula (I) which have the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include compounds of formula (I) in which the carboxyl function has been modified, for example, as a carboxylic acid ester, such as a C_{1-6} alkyl ester.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having a non-pharmaceutically acceptable counterion or associated solvent are within the scope of the present invention having use as intermediates in the preparation of compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically acceptable derivatives.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, salicylates, succinates, lactates, glutarates, glutaconates, acetates, tricarballylates, citrates, fumarates and maleates) and inorganic base salts such as alkali metal salts (for example sodium salts). Hydrochloride salts of the compounds of formula (I) are preferred for certain modes of administration.

Other salts of the compounds of formula (I) include salts formed with trifluoroacetic acid.

Suitable pharmaceutically acceptable solvates of the compounds of formula (I) include hydrates.

The term "alkyl" as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their salts, solvates, and physiologically functional derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures).

The term "halo" means fluoro, chloro, bromo, or iodo.

The term "haloalkyl" as a group or part of a group means an alkyl group as defined above in which one or more hydrogens is replaced by a halo group as defined above and preferably containing one, two, or three halo groups selected from fluoro and chloro.

The term "aryl" means a carbocyclic aromatic ring system. Examples of such groups include phenyl, 1-, or 2-naphthyl. and biphenyl.

The term "hetaryl" means a 5- or 6- membered aromatic ring containing one, two, or three heteroatoms independently selected from nitrogen, oxygen, and sulphur. Examples of such groups include pyrazole and oxadiazole.

By the term "pharmaceutically acceptable derivative" is meant a pharmaceutically acceptable salt, solvate, or physiologically functional derivative of a compound of formula (I) as hereinbefore defined.

Compounds of formula (I) inhibit blood platelet aggregation as demonstrated by studies performed on human washed and resuspended platelets (HRP) using a Born-type optical aggregometer (Born, G.V., 1962, Nature, 194, 927-929). In view of their fibrinogen antagonist activity, the compounds of formula (I) and their pharmaceutically acceptable derivatives are of interest for use in human and veterinary medicine, particularly in the treatment of thrombotic disorders. Particular examples of thrombotic disorders are known in the art and include occlusive vascular diseases such as myocardial infarction, cardiac fatalities, angina, transient ischaemic attacks and thrombotic stroke, arteriosclerosis, vessel wall disease, peripheral vascular disease, nephropathy, retinopathy, postoperative thrombosis, pulmonary embolism, deep vein thrombosis and retinal vein thrombosis. The compounds of formula (I) and their pharmaceutically acceptable derivatives are also of interest for use in the prophylactic treatment of peri- and postoperative complications following organ transplantation (particularly cardiac and renal), coronary artery bypass, peripheral artery bypass, angioplasty, thrombolysis and endarterectomy.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may also be useful for the treatment of other conditions in which the glycoprotein complex Gp IIb/IIIa or other integrin receptors are implicated. Thus, for example, the compounds of formula (I) and their pharmaceutically acceptable derivatives may potentiate wound healing and be useful in the treatment of bone conditions caused or mediated by increased bone resorption. Particular examples of bone diseases are known in the art and include

osteoporosis, hypercalcaemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia and glucocorticoid treatment.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may also be useful for the treatment of certain cancerous diseases, for example, to prevent or delay metastasis in cancer.

According to a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine, particularly for use in the treatment of thrombotic disorders.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated through the Glycoprotein complex GpIIb/IIIa or other integrin receptor.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated through the Glycoprotein complex GpIIb/IIIa or other integrin receptor which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of thrombotic disorders.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a thrombotic disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

It is to be understood that reference to "treatment" includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

It will be appreciated that the compounds of formula (I) and their pharmaceutically acceptable derivatives may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable agents for adjunctive therapy include thrombolytic agents or any other compound stimulating thrombolysis or fibrinolysis and cytotoxic drugs. It is to

be understood that the present invention covers the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in combination with one or more other therapeutic agents.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. The compounds may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch. In a preferred aspect, the invention provides an iontophoretic delivery device (for example, an iontophoretic patch) comprising a compound of formula(I) or a pharmaceutically acceptable derivative thereof, suitably a pharmaceutically acceptable salt thereof, for example, a hydrochloride salt. Iontophoretic devices and systems as such are known in the art, for instance from, WO-A 9116946, WO-A 9116944, WO-A 9116943, WO-A 9115261,W0-A 9115260, WO-A 9115259, WO-A 9115258, WO-A 9115257,WO-A 9115250, WO-A 9109645, W0-A 9108795, WO-A 9004433,WO-A 9004432, WO-A 9003825, EP-A 254965, US 4717378, EP-A 252732 and GB-A 2239803, which are incorporated herein by reference.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory

agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

As stated above, the compounds of formula (I) and their pharmaceutically acceptable derivatives may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent, in particular a thrombolytic agent.

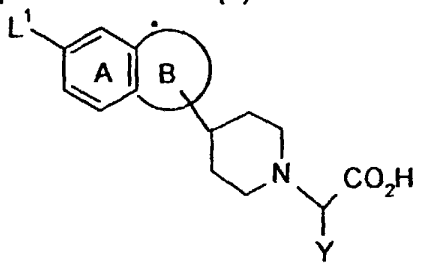
The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of a compound of formula (I) for the treatment of man is 0.01 mg/kg to 30 mg/kg, which may be conveniently administered in 1 to 4 doses. The precise dose employed will depend on the age and condition of the patient and on the route of administration. Thus, for example, a daily dose of 0.1mg/kg to 10mg/kg may be suitable for systemic administration.

Compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure, for example, by the methods described below.

Thus, according to a first process (A), compounds of formula (I) may be prepared by coupling a compound of formula (II)



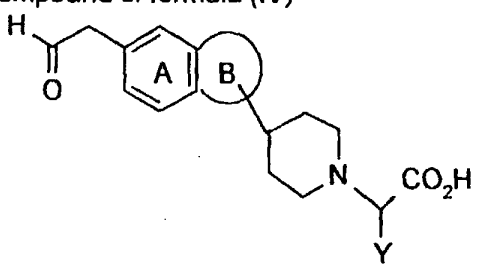
(II)

or a protected derivative thereof wherein L^1 represents a leaving group, for example, chloro, bromo or iodo, or a $-OSO_2CF_3$ group, with the alkene or alkyne of formula (III)

(III)

or a protected derivative thereof wherein:
ring system AB and Y are as defined above; and Z is piperidinyl or quinuclidinyl. This coupling may be effected in the presence of a transition metal catalyst and at elevated temperature. Suitable transition metal catalysts include palladium catalysts, such as a palladium triarylphosphine catalyst. Suitable temperatures are from about 20 to about 160°C, such as 80 to 120°C, or the reflux temperature of the solvent. Conveniently the coupling is effected in the presence of a base, such as a tertiary amine and in a solvent, such as a polar solvent, for example *N*,*N*-dimethylformamide.

According to a further process (B), compounds of formula (I) wherein Z is piperazinyl or a protective derivative thereof may be prepared by reductive alkylation of a compound of formula (IV)



(IV)

or a protected derivative thereof, with piperazine wherein ring system AB and Y are as defined above. This reductive alkylation may be effected in the presence of a suitable reducing agent, for example, sodium triacetoxyborohydride, and in a suitable solvent, such as tetrahydrofuran.

The compounds of formula (IV) may be prepared either (i) from the corresponding aminoalkoxyvinyl compound by treatment with acid; or (ii) oxidation of the corresponding allyl compound, for example, with osmium tetroxide.

According to another process (C) compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) or protected derivatives thereof as precursors.

For example, compounds of formula (I) in which X represents CH_2-CH_2 may be prepared from the corresponding compounds of formula (I) in which X represents CH=CH or C≡C by hydrogenation. The hydrogenation may be effected in the presence of a transition metal catalyst, such as Raney Nickel, or a palladium, platinum or rhodium catalyst. Conveniently the reaction is effected in a solvent, such as an alcohol (e.g. ethanol).

Alternatively, hydrogenation may be effected chemically, for example, by using diimide. Conveniently the diimide is generated *in situ* from a suitable salt, such as diazenedicarboxylic acid, dipotassium salt, and the reaction is effected in the presence of an acid, such as acetic acid, and a solvent, such as an alcohol (e.g. methanol).

A further embodiment of process (C) is conversion of a compound of formula (I) or protected derivative thereof wherein ring B is unsubstituted (ie -L-R° is hydrogen) to a substituted analogue. For example:

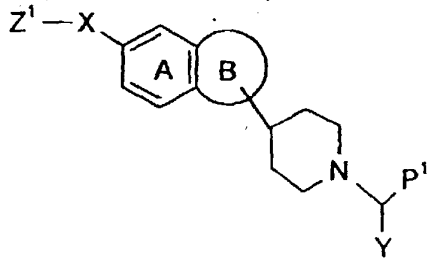
(a) reaction of a compound of formula (I) or a protected derivative wherein -L-R° is hydrogen with a C_{1-10} alkyl halide or an optionally substituted benzyl or phenethyl halide in the presence of a base, such as sodium hydride, in a polar solvent, such as N,N-dimethyl formamide, to afford a compound of formula (I) wherein -L-R° is C_{1-10} alkyl, or optionally substituted benzyl respectively. Similarly, reaction with an acid halide or sulphonyl halide will provide a compound of formula (I) wherein L is C(O) or $S(O)_2$ respectively and reaction with the appropriate isocyanate will provide a compound of formula (I) wherein L is CONH.

(b) a compound of formula (I) wherein -L-R^o is C_{1-6} alkoxycarbonyl may be converted to a compound of formula (I) wherein -L-R^o is hetaryl, for example oxadiazolyl. This conversion may be effected via the corresponding hydrazide via reaction with triethyl ortho acetate, and then cyclisation.

(c) a compound of formula (I) or a protected derivative thereof wherein -L-R^o is C_{1-5} alkoxycarbonyl may be converted to the corresponding amide by reaction with the appropriate amine.

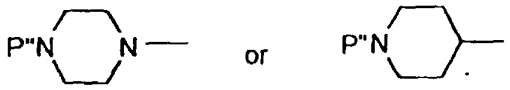
As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the above described processes to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

Another process (D) for preparing compounds of formula (I) thus comprises deprotecting a compound of formula (V)



(V)

wherein Z^1 is quinuclidinyl,

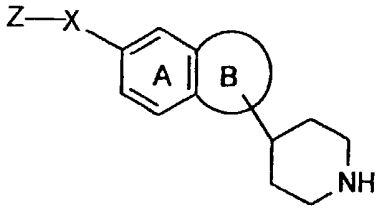


ring system AB, X, and Y are as defined for formula (I); and

P' is a carboxyl group or a protected carboxyl group and P" is hydrogen or an amino protecting group, provided that when P' is a carboxyl group, P" is not hydrogen, and when Z^1 is quinuclidinyl P' is a protected carboxyl group.

Compounds of formula (V) may be prepared by processes (A), (B) or (C) as described above.

Alternatively, compounds of formula (V) wherein Y is hydrogen may be prepared by reacting a compound of formula (VI)



(VI)

or a protected derivative thereof, with a compound of formula (VII)

(VII)

wherein Z, X and ring system AB are as hereinbefore defined, L^2 is a leaving group, for example, chloro, bromo, iodo, or mesylate, and P^1 is a protected carboxyl group.

Suitabiy, the reaction is carried out in the presence of an inorganic base, for example, a bicarbonate, such as sodium bicarbonate; in a polar solvent, for example, N,N-dimethylformamide, at a non-extreme, suitably ambient, temperature.

In a particular embodiment of process (D), compounds of formula (I) may be prepared from protected carboxyl derivatives of compounds of formula (I), ie. compounds of formula (I) wherein P' is a protected carboxyl group. In a further embodiment of this process, compounds of formula (I) may be prepared from protected amino derivatives of compounds of formula (I), ie. compounds of formula (V) wherein P" is an amino protecting group.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W. Green, second edition, (John Wiley and Sons, 1991), which also describes methods for the removal of such groups.

Particular protected carboxyl groups include, for example, carboxylic acid ester groups such as carboxylic acid alkyl or aralkyl esters, for example where the alkyl or aralkyl portion of the ester function is methyl, ethyl, tert-butyl, methoxymethyl, benzyl, diphenylmethyl, triphenylmethyl or p-nitrobenzyl. When the ester is an unbranched alkyl (e.g. methyl) ester deprotection may be effected under conditions of either basic hydrolysis, for example using lithium hydroxide, or acidic hydrolysis, for example using hydrochloric acid. Tert-butyl and triphenylmethyl ester groups may be removed under conditions of acid

hydrolysis, for example using formic or trifluoroacetic acid at room temperature or using hydrochloric acid in acetic acid. Benzyl, diphenylmethyl and nitrobenzyl ester groups may be removed by hydrogenolysis in the presence of a metal catalyst (e.g. palladium).

Particular amino protecting groups include, for example, aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl, t-butoxycarbonyl or trifluoroacetyl groups.

When a particular isomeric form of a compound of formula (I) is desired the required isomer may conveniently be separated using preparative high performance liquid chromatography (h.p.l.c.) applied to the final title compounds of processes (A) to (D) above or applied prior to any final deprotection step in said processes.

Compounds of formula (II) and (III), or protected derivatives thereof, may be prepared using any appropriate methods, such as those described in the examples.

Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention. Compounds of formula (II), for example, {4-[6-bromo-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tert-butyl ester, 3-(1-benzyloxycarbonyl-piperidin-4-yl)-6-bromo-indazole-1-carboxylic acid benzyl ester, [4-(6-bromo-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-acetic acid tert-butyl ester, 5-bromo-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester, and [4-(5-bromo-3-morpholin-4-ylmethyl-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester, are key intermediates and represent a particular aspect of the present invention. The compounds of formula (IV), (V), and (VI) are also an important aspect of the present invention and include 4-{2-[3-(1-tert-butoxycarbonyl-methyl-piperidin-4-yl)-1-(4-carbamoyl-benzyl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester, (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid tert-butyl ester , 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester, 4-{2-[1-(4-fluoro-benzyl)-3-(1-methoxycarbonyl-methyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester, 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-benzo[d]isoxazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester, 4-

{2-[3-(1-tert-butoxycarbonyl-methyl-piperidin-4-yl)-benzo[d]isoxazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester, 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-methoxy-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester , 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-(pyrrolidine-1-carbonyl)-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester,) 4-{2-[1-(1-tert-butoxycarbonyl-methyl-piperidin-4-yl)-3-cyano-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester, 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-morpholin-4-ylmethyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester, and 4-[2-(3-piperidin-4-yl-1H-indazol-6-yl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester acetate.

Conveniently, compounds of the invention are isolated following work-up as acid addition salts, e.g. trifluoroacetate or hydrochloride salts. Pharmaceutically acceptable acid addition salts of the compounds of the invention may be prepared from the corresponding trifluoroacetate salts by exchange of ion using conventional means, for example by neutralisation of the trifluoroacetate salt using a base such as aqueous sodium hydroxide, followed by addition of a suitable organic or inorganic acid, for example, hydrochloric acid. Alternatively, pharmaceutically acceptable acid addition salts may be prepared directly by effecting deprotection with the appropriate organic or inorganic acid, for example, hydrochloric acid. Inorganic base salts of the compounds of the invention may also be prepared from the corresponding trifluoroacetate salts by addition of a suitable strong base such as sodium hydroxide.

Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

The following Examples illustrate the invention but do not limit the invention in any way. All temperatures are in ^{0}C. Thin layer chromatography (T.l.c.) was carried out on silica plates. Preparative high performance liquid chromatography (h.p.l.c.) was carried out using a Dynamax 60Å C18 8mM 25cm x 41.4mm i.d. column eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water and (ii) acetonitrile, the eluant being expressed as the percentage of (ii) present in the solvent mixture, at a flow rate of 45ml per minute. Analytical h.p.l.c. was carried out using a Dynamax 60Å C18 8mM 25 cm x 4.6mm i.d. column eluted with a mixture of solvents consisting of (i) and (iii), 0.05% trifluoroacetic acid in acetonitrile, the eluant being expressed as the

percentage of (iii) present in the solvent mixture, at a flow rate of 1ml per minute. The following abbreviations are used: Me = methyl; Et = ethyl; RT = Retention time; THF = tetrahydrofuran; and DMF = *N,N*-dimethylformamide.

Example 1

Synthesis of {4-[1-(4-carbamoyl-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid

(i) 1-[4-(2,4-Dibromo-benzoyl)-piperidin-1-yl]-ethanone

1,3-Dibromobenzene (65ml, Aldrich) was added to a stirred mixture of 1-acetyl-piperidine-4-carbonyl chloride hydrochloride[0] (21.8g) and aluminium (III) chloride (34.5g) and the mixture heated at 95 - 100° for 1.5h. When cool, the mixture was poured into a mixture of ice-water (50ml) and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution with ether - ethanol (gradient 99:1 to 90: 10) afforded the title compound as an orange oil (16.7g).

T.l.c. SiO_2 (Et_2O:EtOH, 9:1) Rf = 0.23

Ref[0]: EP-A-0 428 437

(ii) (2,4-Dibromo-phenyl)-piperidin-4-yl-methanone hydrochloride

A stirred mixture of 1-[4-(2,4-dibromo-benzoyl)-piperidin-1-yl]-ethanone (11.00g) and aqueous 5M hydrochloric acid (60ml) was heated under reflux under nitrogen for 7h. The mixture was evaporated *in vacuo* to give the title compound as a white solid (10.8g).

T.l.c. SiO_2 (CH_2Cl_2-EtOH-880NH_3, 89:10:1) Rf = 0.17

(iii) (2,4-Dibromo-phenyl)-piperidin-4-yl-methylene-hydrazine

A stirred solution of (2,4-dibromo-phenyl)-piperidin-4-yl-methanone hydrochloride (7.04g), hydrazine (6.0ml, 191 mmol), and ethanol (150ml) was heated under reflux under nitrogen for 16h. The cooled solution was evaporated *in vacuo*, treated with aqueous 1M sodium carbonate (50ml), extracted with ether, and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography over silica gel eluting with dichloromethane-ethanol-880 ammonia (gradient 89:10:1 to 835:150:15) to give the title compound as a cream solid (5.71g).

T.l.c. SiO_2 (CH_2Cl_2-EtOH-880 NH_3, 78:20:2) Rf = 0.13 (minor) and Rf = 0.16 (major)

(iv) 6-Bromo-3-piperidin-4-yl-1H-indazole hydrochloride

A stirred mixture of (2,4-dibromo-phenyl)-piperidin-4-yl-methylene-hydrazine (5.64g), sodium hydride (1.25g, 60% dispersion in oil), and dry DMF (150ml) was heated at 105° under nitrogen for 6.5h. Further sodium hydride (200mg) was added and heating continued for 2h. The mixture was evaporated *in vacuo* acidified to pH 1 by the addition of aqueous 2M hydrochloric acid, and then basified to pH 8 by the addition of aqueous 1M sodium carbonate. The mixture was extracted with ether, and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography over silica gel, eluting with dichloromethane:ethanol:880 ammonia (gradient 89:10:1 to 78:20:2) to give the title compound as a cream-yellow solid (2.50g).
T.l.c. SiO_2 (CH_2Cl_2-EtOH-880NH_3, 78:20:2) Rf = 0.6

(v) [4-(6-Bromo-1H-indazol-3-yl)-piperidin-1-yl]-acetic acid tert-butyl ester

A mixture of 6-bromo-3-piperidin-4-yl-1H-indazole hydrochloride (500mg), tert-butyl bromoacetate (0.29ml), sodium bicarbonate (150mg), and DMF (10ml) was stirred at 23° under nitrogen for 18h. The mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (25ml), and extracted with ethyl acetate. The dried (Na_2SO_4) organic layer was evaporated *in vacuo* onto silica gel. Purification by flash chromatography over silica gel, eluting with dichloromethane - ethanol - 880ammonia (gradient 967:30:3 to 945:50:5) afforded the title compound as fine white crystals (347mg).
T.l.c. SiO_2 (CH_2Cl_2-EtOH-880 NH_3, 945:50:5) Rf = 0.27

(vi) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A mixture of [4-(6-bromo-1H-indazol-3-yl)-piperidin-1-yl]-acetic acid tert butyl ester (1.34g), 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester (0.75g), triethylamine (1.4ml), palladium (ii) acetate (0.050g) and tri(*o*-tolyl)phosphine (0.210g) in DMF (60ml) was stirred at 120° under nitrogen for 16h. The mixture was evaporated *in vacuo* and purified by flash chromatography on silica gel,

eluant ethyl acetate: cyclohexane: triethylamine (50:50:2→100:0:2), to give the title compound as a yellow solid (1.18g).
T.l.c. SiO_2 (CH_2Cl_2 : EtOH: 880 NH_3 95: 5: 0.5) Rf = 0.32

(vii) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1-(4-carbamoyl-benzyl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

Sodium hydride (12.6mg) was added to a stirred solution of 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (150mg) in DMF (5ml) at 23° under nitrogen, and stirring was continued at 22° for 20 min. 4-Bromomethyl-benzamide[1] (67mg) was added and stirring was continued at 22° for 21h. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give a pale yellow solid (179mg). Purification by short path chromatography on silica gel , eluting with dichloromethane: ethanol 880 ammonia 95:5: 0.5, gave a white solid (134mg). Further purification by short path chromatography on silica gel, eluting with CH_2Cl_2: EtOH: 880NH_3 97.5: 2.5: 0.25 gave the title compound as a white solid (104mg).
T.l.c. SiO_2 (CH_2Cl_2: EtOH: 880NH_3 95: 5 : 0.5) Rf = 0.2
REF[1] US Patent 3931268

(viii) {4-[1-(4-Carbamoyl-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate -
A solution 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1-(4-carbamoyl-benzyl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (100mg) in trifluoroacetic acid (4ml) was stirred at 23° under nitrogen for 2.5h. The mixture was evaporated to dryness *in vacuo* to give a colourless gum. Trituration with dry ether gave the title compound a white solid (55mg).
Mass spectrum m/z 502 (MH^+)
Nmr (d^6 DMSO) δ values 8.6,8.3 (2H), 7.92, 7.38 (2H), 7.86-7.78 (3H), 7.68 (1H), 7.32 (1H), 7.22 (2H), 6.35 (1H), 6.4 (1H), 5.67 (2H), 4.11 (2H), 3.7-2.9 (10H), 2.2 (4H), 1.95 (2H), and 1.55 (2H)

Example 2

Synthesis of {4-[1-(4-Carbamoyl-benzyl)-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)

{4-[1-(4-Carbamoyl-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate (0.10g) was hydrogenated at 20% and atmospheric pressure over 10% palladium on charcoal (50% paste with water, 0.05g) for 4h. The catalyst was filtered off and the solvent evaporated *in vacuo* to give a colourless oil (0.074g). Trituration with dry ether gave the title compound as a white solid (0.074g).

Mass spectrum m/z 504 (MH^+)

Analysis Found: C,50.3; H,5.1; N,8.6.

$C_{29}H_{37}N_5O_3.2.9\ CF_3CO_2H$ requires C,50.1; H,4.8; N,8.4.

The following compounds were prepared by methods analogous to those used in Examples 1 and 2:

Example 3

{4-[1-(4-Fluoro-benzenesulfonyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]piperidin-1-yl}-acetic acid trifluoroacetate.

Mass spectrum m/z 527 (MH^+).

Example 4

(4-{1-[2-(4-Fluoro-phenyl)-ethyl]-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid trifluoroacetate.

Mass spectrum m/z 491.5 (MH^+).

Example 5

[4-[1-(4-Nitro-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl]acetic acid trifluoroacetate.

Mass spectrum m/z 504.5 (MH^+).

Example 6

{4-[1-Cyclopentylmethyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate monohydrate.

Mass spectrum m/z 451 (MH^+).

Example 7

{4-[1-(4-Methyl-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate.

Mass Spectrum m/z 473 (MH^+).

Example 8

{4-[1-(4-Pentyloxy-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate.

Mass spectrum m/z 545.1 (MH^+).

Example 9

{4-[1-(4-Bromo-benzoyl-carbonyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate).

Mass spectrum m/z 551.2 [MH^+].

Example 10

{4-[1-(4-Dimethylamino-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate) monohydrate.

Mass spectrum m/z 502 (MH^-).

Example 11

{4-[1-(4-Hydroxy-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid bis(trifluoroacetate) monohydrate.

Mass spectrum m/z 475.3 (MH^+).

Example 12

{4-[1-(4-Cyano-phenyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate monohydrate.

Mass spectrum m/z 470.4 (MH^+).

Example 13

{4-[1-(3,4-Dichloro-phenylcarbamoyl)-6-(2-piperidin-4-yl)-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid bis(trifluoroacetate) monohydrate.

Mass spectrum m/z 556.3 (MH^+).

Example 14

{4-[6-(2-Piperidin-4-yl-(E)-vinyl)-1-(2,2,2-trifluoro-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate.

Mass spectrum m/z 451.4 (MH^+).

Example 15

{4-[1-Methylcarbamoyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate.

Mass spectrum m/z 426 (MH^+).

Example 16

{4-[1-(4-Carbamoyl-benzyl)-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate).

Mass spectrum m/z 504 (MH^+).

Example 17

Synthesis of {4-[6-(2-piperidin-4-yl-(Z)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid.

(i) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(Z)-vinyl}piperidine-1-carboxylic acid tert-butyl ester.

The mother liquors from the preparation of 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(E)-vinyl}piperidine-1-carboxylic acid tert-butyl ester were concentrated to a gum and purified by a combination of crystallisation, column chromatography on silica gel and preparative HPLC to give the title compound as a gum (9mg).

^1H NMR ($CDCl_3$) δ: 1.2-1.5 (2H) m; 1.47 (9H) s; 1.50 (9H) s; 1.69 (2H) m; 2.12 (2H) m; 2.2-2.7 (5H) broad resonances; 2.75 (2H) m; 3.0-3.4 (5H) broad resonances; 4.09 (2H) broad resonance; 5.53 (1H) dd; 6.52 (1H) d; 7.04 (1H) d; 7.28 (1H) s; 7.78 (1H) broad resonance.

(ii) {4-[6-(2-Piperidin-4-yl-(Z)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid salt with deuterium chloride

4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(Z)-vinyl}piperidine-1-carboxylic acid tert-butyl ester (ca. 1mg) was dissolved in 6.6M deuterium chloride in deuterium oxide (0.6ml) to give, after 16h at ambient

temperature, the title compound as a solution in 6M deuterium chloride in deuterium oxide.
^{1}H NMR (20wt% DCl in D_2O) δ: 1.72 (2H) m; 1.97 (2H0 m; 2.48 (5H) m; 3.00 (2H) m; 3.40 (5H) m; 3.91 (2H0 m; 5.74 (1H) dd; 6.64 (1H) d; 7.3 (1H) d (obscured by HOD resonance); 7.59 (1H) s; 8.08 (1H) d.

Example 18

Synthesis of {4-[1-pentyl--6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid.

(i) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (0.84g) in ethanol (80ml) was hydrogenated over 10% palladium on carbon (0.14g) for 4h. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to give the title compound as an ivory solid (0.80g).
Mass spectrum m/z 527 [MH^+].

(ii) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1-pentyl-1H-indazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester (270mg) sodium hydride (25mg of a 60% dispersion in oil), and DMF (10ml) was stirred at 23° under nitrogen for 30 min. A solution of 1-iodopentane (0.075ml) in DMF (1ml) was added and stirring continued for 18h. The mixture was evaporated *in vacuo* treated with aqueous saturated sodium bicarbonate, and extracted with ether. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residual oil purified by flash chromatography over silica gel elution with ethanol - dichloromethane (gradient 1:19 to 1:49) afforded the title compound as a colourless oil (169mg).
T.l.c. SiO_2 (EtOAc-cyclohexane - Et_3N, 34:65:1) Rf = 0.3

(iii) {4-[1-Pentyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

A solution of 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1-pentyl-1H-indazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester(169mg) in trifluoroacetic acid (5ml) was stirred at 23° under nitrogen for 3h. The mixture was evaporated *in vacuo* to give the crude product. This was purified by preparative h.p.l.c. on an Inertsil ODS2 IK5 16416 one inch preparative column. The flow rate was 15.0ml/min and the column eluted with a mixture of solvents consisting of (i) 0.12% trifluoroacetic acid in water and (ii) acetonitrile. The eluant was expressed as the percentage of (ii) in the solvent mixture. The gradient profile was isochratic in (ii) 0% for 5 min, 0 to 55% (ii) in 15 min, isochratic in 55% (ii) for 10 min, 55 to 0% (ii) in 2 min, and isochratic in 0% (ii) for 3 min. The product was triturated with ether (25ml) and filtered off to give the title compound as a white solid (66mg). Preparative h.p.l.c. Rt 15.8 min (on the system and conditions described above)
Mass spectrum m/z 441 (MH^+).

Example 19

Synthesis of (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid.

(i) Tert-butyl [4-[6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1H-indazol-3-yl]-piperidin-1-yl]-acetate.

A mixture of tert-butyl [4-(6-bromo-1H-indazol-3-yl)-piperdin-1-yl]-acetate (394mg), 4-vinyl-1-aza-bicyclo[2.2.2]octane (206mg), palladium (II) acetate (22.4mg), tri-o-tolylphosphine (61mg), triethylamine (0.28ml) and DMF (10ml) was heated at 110° for 20h under nitrogen. After cooling, the solvent was removed *in vacuo* and the residue partitioned between 8% sodium bicarbonate and ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* and the residue purified by flash column chromatography over silica (100g) with dichloromethane - methanol - 0.88 ammonia (29:10:1) eluent to afford the title compound (480mg).
T.l.c. SiO_2 (CH_2Cl_2-MeOH-aq. NH_3 29:10:1) Rf = 0.6

(ii) [4-[6-[2-(1-Aza-bicyclo[2,2,2]oct-4-yl)-(E)-vinyl]-1H-indazol-3-yl]-piperidin-1-yl]-acetic acid trifluoroacetate

Tert-butyl [4-[6-[2-(1-aza-bicyclo[2,2,2]oct-4-yl)-(E)-vinyl]-1H-indazol-3-yl]-piperidin-1-yl]-acetate (303mg) was dissolved in trifluoroacetic acid - water

(9:1,10ml) and allowed to stand for 17h. The solvents were removed *in vacuo* and the residue purified by gradient preparative HPLC (5-45% (ii) over 15 min, RT 12min). to afford the title compound as a colourless solid (168mg).
Assay Found C, 51.1; H, 5.3; N, 8.6
$C_{23}H_{30}N_4O_2$. 2.2.CF_3CO_2H requires: C, 51.0; H, 5.0; N, 8.7%
Mass spectrum; m/z 395.1 (MH^+)

Example 20

Synthesis of (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid.

(i) {4-[6-Bromo-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tert-butyl ester

Sodium hydride (54mg of a 60% dispersion in oil) was added to a stirred solution of [4-(6-bromo-1H-indazol-3-yl)-piperidin-1-yl]-acetic acid tert-butyl ester (500mg) in DMF (17ml) at 23° under nitrogen. After 20 min, a solution of methanesulfonic acid 3-cyclohexyl-propyl ester[2] (279mg) in DMF (2ml) was added and stirring continued for 4h. The mixture was evaporated *in vacuo*, treated with water (30ml), and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residual oil purified by flash chromatography over silica gel. Elution with triethylamine-ether-cyclohexane (gradient 5:50:945 to 1:10:89) afforded the title compound as a colourless oil (466mg).
Mass spectrum m/z 518 (MH^+)
Ref[2]: EP0559345A1

(ii) (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid tert-butyl ester

A stirred mixture of {4-[6-bromo-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tert-butyl ester (428mg), 4-vinyl-1-aza-bicyclo[2.2.2]octane (198mg), palladium (II) acetate (19mg), tri-o-tolylphosphine (50mg), triethylamine (0.34ml), and DMF (8ml) was heated at 105° under nitrogen for 15h. When cool, the mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (25ml), and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution

with dichloromethane-ethanol-880 ammonia (gradient 945:50:5 to 927:70:7) afforded the title compound as a yellow oil (198mg).

(iii) (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid tris(trifluoroacetate) monohydrate

A solution of (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid tert-butyl ester (193mg) in trifluoroacetic acid (5ml) was kept at 23° for 3h. The solution was evaporated *in vacuo* and the residue purified by preparative HPLC using, standard conditions, gradient profile 10-90% (ii) in 25 min, RT 15.4min. The collected eluant was evaporated *in vacuo* and the residue triturated with ether to give the title compound as a white solid (115mg).

Mass spectrum m/z 519.4 (MH^+)

Analysis Found: C,56.5; H,6.5; N,7.3.

$C_{32}H_{46}N_4O_2.3CF_3CO_2H.H_2O$ requires C,56.5; H,6.6; N,7.3%.

The following compounds were prepared by methods analogous to those used in Example 20:

Example 21

[4-[6-[2-(1-Aza-bicyclo[2,2,2]oct-4-yl)-(E)-vinyl]-1H-indazol-3-yl]-piperidin-1-yl]-acetic acid trifluoroacetate.

Mass spectrum; m/z 395.1 (MH^+).

Example 22

4-[6-[2(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(4-fluoro-benzyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate.

Analysis Found: C,52.9; H,4.7; N,6.95.

$C_{30}H_{35}FN_4O_2.2.6C_2HF_3O_2$ requires C,52;9; H,4.7; N,7.0%.

Example 23

(4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(4-tert-butyl-benzenesulfonyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid bis(trifluoroacetate) monohydrate

Analysis Found: C,53.2; H,5.4; N,6.6.

$C_{33}H_{42}N_4O_4S.2CF_3CO_2H.H_2O$ requires C,53.1; H,5.5; N,6.7

Example 24

Synthesis of {4-[6-(2-piperazin-1-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid.

(i) 3-(1-Benzyloxycarbonyl-piperidin-4-yl)-6-bromo-indazole-1-carboxylic acid benzyl ester

2N aqueous sodium hydroxide (20ml) was added dropwise to a stirred suspension of 6-bromo-3-piperidin-4-yl-1H-indazole hydrochloride (3.17g) and benzyl chloroformate (3.56ml) in dichloromethane (100ml) under nitrogen, and stirring was continued for 16h at 23°. The mixture was partitioned between water (200ml) and dichloromethane; the organic layers were washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification by dry flash chromatography on silica gel, eluting with ether: cyclohexane 10: 90-50:50, gave the title compound as a white solid (3.22g).

T.l.c. SiO_2 (Ether: cyclohexane 50:50) Rf = 0.3

(ii) 6-Allyl- 3-(1-benzyloxycarbonyl-piperidin-4-yl)-indazole-1-carboxylic acid benzyl ester

3-(1-Benzyloxycarbonyl-piperidin-4-yl)-6-bromo-indazole-1-carboxylic acid benzyl ester (3.1g) was heated under reflux with allyltributyltin (2.08ml) and tetrakis(triphenylphosphine) palladium (O) (148mg) in dry toluene (80ml) with stirring under nitrogen for 40h. The mixture was partitioned between ethyl acetate (100ml) and 10% aqueous potassium fluoride (50ml). The white precipitate was filtered off, the layers separated, and the organic layer washed with more 10% aqueous potassium fluoride (50ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a pale yellow semi-solid (3.85g). Purification by flash chromatography on silica gel, eluting with ether:hexane 40:60, gave the title compound as a colourless oil (2.04g).

T.l.c. SiO_2 (ether:cyclohexane 50:50) Rf = 0.4.

(iii) 3-(1-Benzyloxycarbonyl-piperidin-4-yl)-6-[2-(4-tert-butoxycarbonyl-piperazin-1-yl)-ethyl]-indazole-1-carboxylic acid benzyl ester

6-Allyl- 3-(1-benzyloxycarbonyl-piperidin-4-yl)-indazole-1-carboxylic acid benzyl ester (2.0g) was treated at 0° under nitrogen with osmium tetroxide (2.5 wt % solution in t-butanol, 1.03ml) in tetrahydrofuran (40ml) and water (10ml), and the

mixture was stirred at 0° under nitrogen for 1.75h. Sodium periodate (1.69g) was added and stirring was continued at 22° for 3.5h. The mixture was diluted with ether (100ml), the solution decanted from a white precipitate, and the mother liquor evaporated *in vacuo*. The residue was dissolved in tetrahydrofuran (50ml), and sodium triacetoxyborohydride (3.4g) and acetic acid (1.35ml) added. The mixture was stirred at 22° for 16h, basified with 8% aqueous sodium bicarbonate (100ml) and extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil. Purification by flash chromatography on silica gel, eluting with CH_2Cl_2:EtOH:880NH_3 95:5:0.5, gave the title compound as a brown foam (1.92g). Further purification by dry flash chromatography on silica gel, eluting with cyclohexane:ethyl acetate 20:80-0:100, gave the title compound as a white foam (1.10g; 41%).
T.l.c. SiO_2 (EtOAc) Rf = 0.25

(iv) 4-[2-(3-Piperidin-4-yl-1H-indazol-6-yl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester acetate

3-(1-Benzyloxycarbonyl-piperidin-4-yl)-6-[2-(4-tert-butoxycarbonyl-piperazin-1-yl)-ethyl]-indazole-1-carboxylic acid benzyl ester (1.05g) was hydrogenated at 22° and atmospheric pressure over 5% palladium on carbon (50% paste with water, 200mg) in ethanol (20ml) and ethyl acetate (50ml) containing glacial acetic acid (0.195ml) for 16h. The catalyst was filtered off and the solvent evaporated *in vacuo* to give the title compound as a white solid (0.69g).
T.l.c.SiO_2 (CH_2Cl_2:EtOH:880NH_3 78:20:2) Rf=0.1

(v) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester

t-Butylbromoacetate (0.064ml) was added to a stirred suspension of 4-[2-(3-piperidin-4-yl-1H-indazol-6-yl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester acetate (200mg) and sodium bicarbonate (71mg) in dry N,N-dimethylformamide (5ml) at 22° under nitrogen, and stirring was continued at room temperature for 16h. The slightly cloudy solution was poured into water (50ml) and extracted with ethyl acetate. The organic layers were washed with 50:50 brine:water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a white solid (181mg). Purification by dry flash chromatography on silica gel, eluting with

dichloromethane:ethanol:880 ammonia 98:2:0.2 - 93:7:0.7, gave the title compound as a white solid (139mg).
T.l.c. SiO_2 (CH_2Cl_2:EtOH:880NH_3 89:10:1) Rf=0.6

(vi) {4-[6-(2-Piperazin-1-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)
4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester (134mg) was stirred at 22° under nitrogen with trifluoroacetic acid (5ml) for 6.5h. The solvent was evaporated *in vacuo* and the residue triturated with dry ether to give the title compound as a white solid (158mg).
Mass Spectrum m/z 372 (MH^+)
Analysis Found: C,42.1; H,4.6; N,9.1.
$C_{20}H_{29}N_5O_2$.3.5 CF_3COOH requires C,42.1; H,4.25; N,9.1.

Example 25
Synthesis of {4-[1-(4-fluoro-benzyl)-6-(2-piperazin-1-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid.
(i) 4-{2-[3-(1-Methoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester
4-[2-(3-Piperidin-4-yl-1H-indazol-6-yl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester acetate (420mg) was stirred at 23° under nitrogen with methyl bromoacetate (0.085ml) and sodium bicarbonate (151mg) in dry N,N-dimethylformamide (15ml) for 16h. The mixture was poured into water (60ml) and extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound as a white solid (446mg).
Mass Spectrum m/z 486 (MH^+)

(ii) 4-{2-[1-(4-Fluoro-benzyl)-3-(1-methoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester
Sodium hydride (60% dispersion in oil, 23mg) was added to a stirred solution of 4-{2-[3-(1-methoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester (220mg) in dry N,N-dimethylformamide (5ml) at 23° with stirring under nitrogen, and stirring was

continued at 23° for 40 min. 4-Fluorobenzyl bromide (0.057ml) was added and stirring was continued at 23° for 16h. The mixture was poured into water (50ml) and extracted with ethyl acetate; the organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give a colourless gum. Purification by short path chromatography on silica gel, eluting with dichloromethane:ethanol:880 ammonia 99:1:0.1-95:5:0.5, gave the title compound as a colourless gum (58mg).

T.l.c. SiO_2 (CH_2Cl_2:EtOH:880NH_3 95:5:0.5) Rf = 0.7.

(iii){4-[1-(4-Fluoro-benzyl)-6-(2-piperazin-1-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid tetrahydrochloride

A solution of the 4-{2-[1-(4-fluoro-benzyl)-3-(1-methoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester (58mg) in 2N hydrochloric acid (5ml) was stirred at 23° under nitrogen for 20h. The mixture was evaporated to dryness *in vacuo* and the residue triturated with dry ether to give a cream solid (40mg). 30mg of this solid was heated at 80° with 2N hydrochloric acid (5ml) for 66h. The mixture was evaporated to dryness *in vacuo* and the residue triturated with dry ether to give the title compound as a white solid (24mg).

Mass spectrum m/z 480.5 (MH^+)

Analysis Found: C,50.0; H,6.3; N,10.5.

$C_{27}H_{34}N_5O_2F.4HCl.H_2O$ requires C,50.4; H,6.3; N,10.9.

Example 26

Synthesis of (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid trifluoroacetate

(i) 1-[4-(2,4-Dibromo-benzoyl)-piperidin-1-yl]-ethanone

1,3-Dibromobenzene (65ml) was added to a stirred mixture of 1-acetyl-piperidine-4-carbonyl chloride hydrochloride (21.8g) and aluminium (III) chloride (34.5g) and the mixture heated at 95 - 100° for 1.5h. When cool, the mixture was poured into a mixture of ice-water (50ml) and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution with ether - ethanol (gradient 99:1 to 90: 10) afforded the title compound as an orange oil (16.7g).

T.l.c. SiO_2 (Et_2O - EtOH, 9:1) Rf = 0.23

(ii) (2,4-Dibromo-phenyl)-piperidin-4-yl-methanone E-oxime

A stirred mixture of the 1-[4-(2,4-dibromo-benzoyl)-piperidin-1-yl]-ethanone (7.72g), hydroxylamine hydrochloride (6.89g), and pyridine (200ml) was heated at 105° under nitrogen for 16h. When cool, aqueous 1M sodium carbonate (100ml) was added and the mixture evaporated *in vacuo*. Water (200ml) was added and the mixture filtered. The precipitate was dissolved in hot methanol (200ml) and adsorbed onto silica gel (50ml). The resultant silica was purified by flash chromatography over silica gel, eluting with dichloromethane - ethanol - 880 ammonia (gradient 89:10:1 to 725 : 250 : 25) to give the title compound as a white crystalline solid (5.56g).

Mass spectrum *m/z* 363 (MH^+)

(iii) 6-Bromo-3-piperidin-4-yl-benzo[d]isoxazole

A stirred mixture of (2,4-dibromo-phenyl)-piperidin-4-yl-methanone E-oxime (5.56g), sodium hydride (921 mg of a 60% dispersion in oil), and DMF (120ml), was heated at 100° under nitrogen for 0.5h. The cooled mixture was evaporated *in vacuo* and treated with water (10ml) under nitrogen. The mixture was acidified to pH1 by the addition of aqueous 2M hydrochloric acid (25ml), and then basified to pH 8 by the addition of aqueous saturated sodium bicarbonate. The mixture was extracted with ether and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography over silica gel, eluting with dichloromethane - ethanol - 880 ammonia (gradient 945:50:5 to 863:125:12) to give the title compound as a white solid (2.54g).

T.l.c. SiO_2 (CH_2Cl_2 - EtOH - 880 NH_3, 78:20:2) Rf = 0.22

(iv) [4-(6-Bromo-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-(4-chloro-phenyl)-acetic acid ethyl ester

A mixture of 6-bromo-3-piperidin-4-yl-benzo[d]isoxazole (1.50g), bromo-(4-chloro-phenyl)-acetic acid ethyl ester[3] (1.70g), potassium carbonate (1.48g), and acetonitrile (30ml) was stirred under nitrogen for 3h under reflux. The cooled mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (50ml), and extracted with ethyl acetate. The combined, dried

(Na_2SO_4) organic extracts were evaporated *in vacuo* onto silica gel and the resultant silica applied as a plug to a flash column of silica gel. Gradient elution with ethyl acetate - cyclohexane (gradient 1:19 to 1:9) afforded the title compound as a pale yellow oil (2.04g).

T.l.c. SiO_2 (CH_2Cl_2) Rf = 0.10

REF[3] JW. Epstein *et al*, J. Med. Chem., 1981, 24, 481.

(v) (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid ethyl ester

A stirred mixture of 4-vinyl-1-aza-bicyclo[2.2.2]octane[4] (75mg), [4-(6-bromo-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-(4-chloro-phenyl)-acetic acid ethyl ester (261 mg), lithium chloride (23mg), triethylamine (0.23ml), palladium (II) acetate (8 mg), tri-o-tolylphosphine (35mg) and DMF (5ml) was heated at 105° under nitrogen for 18h. The cooled mixture was evaporated *in vacuo* and treated with aqueous saturated sodium bicarbonate (20ml). The mixture was extracted with ethyl acetate, and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography over silica gel, eluting with dichloromethane - ethanol - 880 ammonia (gradient 945:50:5 to 89:10:1) to give the title compound as a colourless liquid (37mg).

T.l.c. SiO_2 (CH_2Cl_2-EtOH-880NH_3, 89:10:1) Rf = 0.14

REF[4] : E. Ceppi *et al*, Helv. Chem. Acta, 1974, 57, 2332.

(vi) (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid trifluoroacetate

A stirred mixture of (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid ethyl ester (292mg), potassium carbonate (290mg), ethanol (20ml), and water (8ml) was heated under reflux under nitrogen for 16h. The cooled mixture was treated with aqueous 2M - hydrochloric acid (2.2ml) and the solution evaporated *in vacuo*. The residue was purified by preparative h.p.l.c. (gradient profile 10-90% (ii) in 25 min, RT14.1 min) and the collected eluant was evaporated *in vacuo*. A solution of the resultant product in water (50ml) was freeze-dried to give the title compound as a white solid (181mg).

Analytical h.p.l.c. (gradient profile 10-90% (ii) in 25min) R_t 13.3 min.

Analysis Found: C, 52.0; H, 4.8; N, 5.5

$C_{29}H_{32}ClN_3O_2$. $2C_2HF_3O$. $1.24H_2O$ requires: C, 52.4; H, 4.9; N, 5.55%

Example 27

Isomer a: (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid trifluoroacetate

Isomer b: (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid trifluoroacetate

(i) [4-(6-Bromo-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-(4-chloro-phenyl)-acetic acid tert-butyl ester

A mixture of 6-bromo-3-piperidin-4-yl-benzo[d]isoxazole (4.77g), a-bromo-4-chlorobenzeneacetic acid, 1,1-dimethylethyl ester (5.96g), and potassium carbonate (4.69g) in DMF (100ml) was stirred at 23° under nitrogen for 2.5h. The mixture was evaporated *in vacuo*, treated with water (50ml), and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution with ethyl acetate-cyclohexane (gradient 3:97 to 10:90) afforded the title compound (7.50g) as an off-white solid.
Mass spectrum m/z 507 (MH^+)

(ii) (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid tert-butyl ester

A mixture of [4-(6-bromo-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-(4-chloro-phenyl)-acetic acid tert-butyl ester (5.7g), 4-vinyl-1-aza-bicyclo[2.2.2]octane (1.93g), triethylamine (4.71ml), tri-*o*-tolylphosphine (686mg) and palladium (II) acetate (254mg) in dry DMF (110ml) was stirred at 120° under nitrogen for 6h. The solvent was removed *in vacuo* to give a brown gum. Purification by flash chromatography on silica gel eluting with dichloromethane:ethanol:0.88 aqueous ammonia (200:10:1) followed by (100:10:1) as the eluant gave the title compound as a pale brown solid (4.1g).
Tlc, SiO_2 (CH_2Cl_2: EtOH: 880 NH_3 100:10:1) Rf = 0.30

(iii) Isomer a: (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid tert-butyl ester

A sample of (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid tert-butyl ester (300mg) was

purified by preparative h.p.l.c. (stationary phase Chiralpak AD. Lot No. 57-47-20728; eluant ethanol:heptane (1:1), flow = 15ml/min, detection wavelength 280nm) to give the title compound as a yellow solid (125mg).
Analytical h.p.l.c. (stationary phase Chiralpak AD, No. 098-017-41011, eluant ethanol:heptane (1:1), flow = 1.0ml/min, detection wavelength 280nm RT = 6.52 min.).

(iv) Isomer a: (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid trifluoroacetate
A solution of (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid tert-butyl ester, isomer a, (100mg) in trifluoroacetic acid: water (9:1; 5ml) was stirred at 20° under nitrogen for 7h. The solvent was removed *in vacuo* to give a yellow oil which was stirred with dry ether for 2h. The solid obtained was dried *in vacuo* at 37° for 4h, to give the title compound as a cream solid (110mg).
Analytical h.p.l.c. (stationary phase Chiralpak AD No. 098-017-41011, ethanol:Et_3N:heptane (47:3:50), temp. 40° flow = 1.0ml/min, detection wavelength 280nm, RT= 7.22min.).
Mass Spectrum m/z 506 (MH^+)

(v) Isomer b: (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid tert-butyl ester
A sample of (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid tert-butyl ester (300mg) was purified by preparative h.p.l.c. (stationary phase Chiralpak AD. Lot No. 57-47-20728; eluant ethanol:heptane (1:1), flow = 15ml/min, detection wavelength 280nm) to give the title compound as a yellow solid (125mg).
Analytical h.p.l.c. (stationary phase Chiralpak AD, No. 098-017-41011, eluant ethanol:heptane (1:1), flow = 1.0ml/min, detection wavelength 280nm RT = 22.2 min).

(vi) Isomer b: (4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid trifluoroacetate
A solution of (4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid tert-butyl ester, isomer b, () in

trifluoroacetic acid: water (9:1; 5ml) was stirred at 20° under nitrogen for 7h. The solvent was removed *in vacuo* to give a yellow oil which was stirred with dry ether for 2h. The solid obtained was dried *in vacuo* at 37° for 4h, to give the title compound as a cream solid (110mg).

Analytical h.p.l.c. (stationary phase Chiralpak AD No. 098-017-41011, ethanol:Et_3N:heptane (47:3:50), temp. 40° flow = 1.0ml/min, detection wavelength 280nm, RT = 10.7min).
Mass. Spec. m/z 506 (MH^+)

Example 28

Synthesis of {4-[6-(2-piperidin-4-yl-(E)-vinyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid.

(i) [4-(6-Bromo-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-acetic acid tert-butyl ester

A mixture of 6-bromo-3-piperidin-4-yl-benzo[d]isoxazole (1.11g), tert-butyl bromoacetate (0.64ml), sodium bicarbonate (332mg), and dry DMF (20ml) was stirred at 23° under nitrogen for 18h. The mixture was evaporated *in vacuo*, treated with water (20ml) and aqueous saturated sodium bicarbonate (20ml). The mixture was extracted with dichloromethane and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residual oil was purified by flash chromatography over silica gel eluting with dichloromethane:ethanol:0.88 ammonia (967:30:3) to give the title compound as cream crystals.
Mass spectrum m/z 395 (MH^+)

(ii) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-benzo[d]isoxazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester (564mg), the [4-(6-bromo-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-acetic acid tert-butyl ester (855mg), palladium (II) acetate (26mg), tri-(o-tolyl)phosphine (94mg), lithium chloride (94mg), DMF (8.5ml), and triethylamine (0.6ml) was stirred at 108° in an autoclave under nitrogen for 16h. When cool, the mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (50ml), and extracted with dichloromethane. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* onto silica gel and the resultant silica applied

as a plug to a flash column of silica gel. Gradient elution with ethyl acetate:cyclohexane (gradient 1:4 to 1:2) gave the cis isomer.
Further elution gave the title compound as a pale yellow gum (501mg).
Mass spectrum m/z 526 (MH^+)

(iii) {4-[6-(2-Piperidin-4-yl-(E)-vinyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid bis(trifluoroacetate)
A solution of 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-benzo[d]isoxazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (220mg) in trifluoroacetic acid (5ml) was kept at 23° under nitrogen for 2.5h. The solution was evaporated *in vacuo*, and the residue triturated with ether (12ml) to give the title compound as a cream solid (220mg).
Mass spectrum m/z 370.2 (MH^+)
Analysis Found: C,49.5; H,4.9; N,6.8.
$C_{21}H_{27}N_3O_3.2CF_3CO_2H.0.57H_2O$ requires C,49.4; H,5.0; N,6.9%.

Example 29
Synthesis of {4-[6-(2-piperidin-4-yl-ethyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid
(I) 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-benzo[d]isoxazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester
To a stirred solution of 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-benzo[d]isoxazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (300mg) in methanol (6ml) at 8° under nitrogen was added six portions of dipotassium azodicarboxylate[5] (6x330mg) over 3 days, followed after each addition by the slow addition of a solution of acetic acid (0.2ml) in methanol (3ml) over 8h. Further dipotassium azodicarboxylate was added (1.00g) and three additions of a solution of acetic acid (3x0.2ml) in methanol (3x0.8ml) was added over 3h periods over 3 days. The mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (30ml), extracted with dichloromethane, and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography over silica gel and elution with ethyl acetate:cyclohexane (gradient 1:3 to 1:2) afforded the title compound as a colourless oil (205mg).
Mass spectrum m/z 528 (MH^+)

REF[5]: Organic Reactions, 1991, 40, 103.

(ii) {4-[6-(2-Piperidin-4-yl-ethyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid bis(trifluoroacetate)

4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-benzo[d]isoxazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester (194mg) was stirred in trifluoroacetic acid (10ml) and water (1ml) for 3h. The mixture was evaporated *in vacuo* and the residue purified by preparative HPLC using the standard conditions, gradient profile 10-20% (ii) in 10 min, 20% (ii) isochratic for 7 min., to give a yellow oil RT 16.5 min. This was co-evaporated with ether to give the title compound as fine white hygroscopic crystals (51mg).

Mass spectrum m/z 372 (MH^+)

Analysis. Found: C,49.0; H,5.3; N,6.6.

$C_{21}H_{29}N_3O_3.2CF_3CO_2H.0.7H_2O$ requires C,49.05; H,5.3; N,6.9%.

Example 30

Synthesis of {4-[6-(2-piperazin-1-yl-ethyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl-acetic acid.

(i) (4-{6-[2-(2-Dimethylamino-ethoxy)-(Z)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-acetic acid tert-butyl ester

A mixture of [4-(6-bromo-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-acetic acid tert-butyl ester (2.68g), dimethyl-(2-vinyloxy-ethyl)-amine[6] (3.12g), tetra-n-butylammonium chloride (1.88g), palladium (II) bis(benzonitrile) dichloride (130mg), potassium carbonate (1.87g), and DMF (20ml) were heated at 85° under nitrogen in an autoclave for 18h. When cool, the mixture mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (30ml), and extracted with dichloromethane. The combined, dried (Na_2SO_4) organic extracts were evaporated and the residue purified by flash chromatography over silica gel. Gradient elution with dichloro-methane:ethanol:0.88 ammonia (gradient 100:0:0→97:3:0→967:30:3) afforded the title compound as a golden oil (1.32g).

Mass spectrum m/z 430 (MH^+)

REF[6]: C-M. Andersson, *et al.*, J. Org. Chem., 1990, 55, 5757.

(ii) {4-[6-(2-Piperazin-1-yl-ethyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid tetrakis(trifluoroacetate)

A solution of (4-{6-[2-(2-dimethylamino-ethoxy)-(Z)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-acetic acid tert-butyl ester (500mg) in sulphuric acid (90%, 1.25ml) and water (3.75ml) was kept at 23° under nitrogen for 2 days. Solid sodium bicarbonate was added to adjust the acidity to pH8. Water (5ml), acetic acid (1.0ml), piperazine (200mg), and sodium triacetoxyborohydride (730mg) were added and stirring continued for 4 days. The mixture was filtered and purified by preparative HPLC using standard conditions, gradient profile 10-40% (ii) in 17 min, to give impure product RT 8.5 min. This was further purified by preparative HPLC in exactly the same way to give the title compound.

Analysis Found: C,40.6; H,4.2; N,7.0.

$C_{20}H_{28}N_4O_3.4CF_3CO_2H$ requires C,40.6; H,3.9; N,6.8%.

Example 31

Synthesis of [4-[3-methoxy-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid.

(i) 5-Bromo-2-nitro-2H-indazole

To stirred acetic anhydride (410ml) at -5° was added, dropwise, fuming nitric acid (8.5ml). After 20 min. the solution was cooled to -15° and 5-bromoindazole (7.70g) was added portionwise maintaining the temperature at -15°. The mixture was stirred at -15° for 2h, added to iced water (1l), and vigorously stirred for a further 2h. The solid was collected by filtration and was partitioned between diethyl ether (500ml) and 5M aqueous sodium hydroxide (350ml). The aqueous layer was extracted with diethyl ether and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as an orange solid (7.45g).

Mass spectrum m/z 243 (MH^+)

(ii) 5-Bromo-3-methoxy-1H-indazole

To a stirred solution of 5-Bromo-2-nitro-2H-indazole (2.80) in methanol (15ml) was added sodium methoxide (1.38g) and this was stirred at 19° for 5h. The mixture was concentrated *in vacuo* and partitioned between dichloromethane and water. The aqueous was re-extracted with dichloromethane and the combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in*

vacuo. The residue was purified by flash chromatography over silica gel and elution with ethyl acetate : cyclohexane (gradient 10% to 15%) afforded the title compound as a cream solid (1.55g, 59%).
Mass Spectrum m/z 229 (MH^+)

(iii) 4-(5-Bromo-3-methoxy-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester

5-Bromo-3-methoxy-1H-indazole (1.53g), 4-Methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester (2.45g) and potassium carbonate (2.80g) were stirred in DMF (20ml) and this was heated to 100° for 6h. Further 4-Methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester (0.38g) was added and heated at 100° for a further 16 hours. The reaction mixture was concentrated *in vacuo* and then partitioned between dichloromethane and water. The aqueous was re-extracted with dichlormethane, and the combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel and elution with ethyl acetate : cyclohexane (1:9) afforded the title compound as a cream solid (1.80g).
Mass Spectrum m/z 412 (MH^+)

(iv) 5-Bromo-3-methoxy-1-piperidin-4-yl-1H-indazole

4-(5-Bromo-3-methoxy-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (1.80g) was dissolved in trifluoroacetic acid (15ml) and this was stirred at 19° for *ca* 1.5h. The reaction mixture was concentrated *in vacuo* and partitioned between dichloromethane and 0.5M sodium hydroxide. The layers were separated and the aqueous was re-extracted with dichloromethane. The combined organics were washed with brine and concentrated *in vacuo* to afford the title compound as a yellow solid (1.39g).
Mass Spectrum m/z 312 (MH^+).

(v) [4-(5-Bromo-3-methoxy-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester

5-Bromo-3-methoxy-1-piperidin-4-yl-1H-indazole (1.36g) sodium bicarbonate (0.66g) and *tert*-butylbromoacetate (0.68ml) were stirred in DMF at 19° for 20h. The reaction mixture was concentrated *in vacuo* and partitioned between

dichlormethane and water. The layers were separated and the aqueous was re-extracted with dichloromethane and the combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel and elution with ethyl acetate : cyclohexane (3:20) afforded the title compound as a yellow solid (1.56g).
Mass Spectrum m/z 426 (MH^+).

(vi) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-methoxy-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

[4-(5-Bromo-3-methoxy-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester (0.50g), 4-Vinyl-piperidine-1-carboxylic acid tert-butyl ester (0.274g), palladium (II) acetate (0.021g), tri-o-tolyphosphine (0.057g) and triethylamine (0.49ml) were stirred in DMF (2.5ml) and was heated to 110°C for 16h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and aqueous sodium bicarbonate. The layers were separated and the aqueous was re-extracted with ethyl acetate. The combined organics were concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel and elution with ethyl acetate : cyclohexane (1:3) afforded the title compound as a yellow solid (0.34g).
Mass Spectrum m/z 555 (MH^+).

(vii) {4-[3-Methoxy-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)

4-{2-[1-(1-*tert*-Butoxycarbonylmethyl-piperidin-4-yl)-3-methoxy-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid *tert*-butyl ester (0.33g) was dissolved in trifluoracetic acid (10ml) and this was stood at 19° for 5h. The reaction mixture was concentrated *in vacuo*, and the residue was triturated with diethyl ether. The solid obtained was further purified by preparative hplc to afford the title compound as a white solid (0.18g).
Mass Spectrum m/z 399 (MH^+).

Example 32

Synthesis of {4-[3-methoxy-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)

A solution of {4-[3-methoxy-5-(2-piperidin-4-yl-E-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate) (95mg) in water (10ml) was added to 10% palladium-on-carbon (containing 50% of water, 40mg) and the mixture stirred under hydrogen for 3.25h. The catalyst was filtered off, washed with water, and the filtrate treated with trifluoroacetic acid (2 drops), and evaporated *in vacuo*. The residue was triturated with ether (10ml) to give the title compound as a fine white powder (83mg).
Mass spectrum m/z 401.1 (MH^+).
Analysis. Found: C, 42.8 ; H, 4.6 ; N, 7.1 ;
$C_{26}H_{37}N_5O_3.3C_2HF_3O_2.H2O$ requires C, 43.2 ; H, 5.05 ; N, 7.2 %.

The following compounds were made by methods analogous to those used in Examples 31 and 32:

Example 33
{4-[5-(2-Piperidin-4-yl-(E)-vinyl)-3-pyrazol-1-yl-indazol-1-yl]-piperidin-1-yl}-acetic acid bis(trifluoroacetate).
Mass spectrum m/z 435 (MH^+).

Example 34
{4-[5-(2-Piperidin-4-yl-(E)-vinyl)-3-pyrrolidin-1-yl-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate).
Mass spectrum m/z 438 (MH^+).

Example 35
{4-[3-Morpholin-4-yl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate).
Mass spectrum m/z 454 (MH^+).

Example 36
Synthesis of {4-[5-(2-piperidin-4-yl-(E)-vinyl)-3-(pyrrolidine-1-carbonyl)-indazol-1-yl]piperidin-1-yl}acetic acid.

(i) 5-Bromo-1-(1-tert-butoxycarbonyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester

5-Bromo-1H-indazole-3-carboxylic acid[7], methyl ester (35.8g) in dry THF (400ml) containing 4-methanesulphonyloxy-piperidine-1-carboxylic acid tert-butyl ester[8] (40.9g) was treated with potassium t-butoxide (15.75g) and stirred at reflux under nitrogen for 24h. When cool, the mixture was evaporated *in vacuo* and the residue treated with aqueous saturated ammonium chloride (400ml). The mixture was extracted with ethyl acetate and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* onto silica gel. The resultant silica was applied as a plug to a flash column of silica gel, eluting with cyclohexane:ethyl acetate (gradient 19:1 to 3:1) to give firstly an isomer followed by the title compound (22.8g).

T.l.c. SiO_2 (cyclohexane:EtOAc, 7:3) Rf - 0.29; detection u.v.

REF[7] G.A. Bistrocchi et al., Farmaco. Ed. Sci., 1981, 36, 315.

REF[8] EP-A-0 560 268 A1.

(ii) 5-Bromo-1-piperidin-4-yl-1H-indazole-3-carboxylic acid methyl ester bis(trifluoroacetate)

Trifluoroacetic acid (100ml) was added to 5-bromo-1-(1-tert-butoxycarbonyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester (22.75g) at 23° during 1 min. After 1h, the mixture was evaporated *in vacuo* and the co-evaporated with dichloromethane to give the title compound (28.05g) as a light yellow solid.

T.l.c. SiO_2 (CH_2Cl_2:EtOH:880NH_3, 89:10:1), Rf 0.18 detection, u.v.

(iii) 5-Bromo-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester

A solution of 5-bromo-1-piperidin-4-yl-1H-indazole-3-carboxylic acid methyl ester bis(trifluoroacetate) (28.05g) and tert-butylbromoacetate (7.3ml) in DMF (500ml) was treated with diisopropylethylamine (25.9ml) under nitrogen with stirring at 23° and kept for 4 days. Further tert-butylbromoacetate (1.4ml), followed by diisoproplyethylamine (5.0ml) were added and stirring continued for 2h. The mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (400ml), and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue crystallised from ethyl acetate to give the title compound (13.43g).

T.l.c. SiO_2 (Cyclohexane:EtOAc, 7:3) Rf 0.17.

(iv) 1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-5-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-(E)-vinyl]-1H-indazole-3-carboxylic acid methyl ester

A mixture of 5-bromo-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester (13.43g), 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester(6.90g), palladium (II) acetate (666mg), tri-o-tolylphosphine (1.81g), triethylamine (12.4ml), and DMF (200ml) was stirred at 120° under nitrogen for 15h. When cool, the mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (200ml), and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution with dichloromethane:ethanol:880 ammonia (gradient 989:10:1 to 978:20:2) afforded impurities, followed by the pure title compound as a light orange foam (8.94g).

T.l.c. SiO_2 (CH_2Cl_2:EtOH:880NH_3, 978:20:2) Rf 0.14.

(v) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-(pyrrolidine-1-carbonyl)-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A solution of 1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-5-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-(E)-vinyl]-1H-indazole-3-carboxylic acid methyl ester (600 mg), pyrrolidine (1.8ml), and THF (7 ml) were heated in a reacti-vial for 28 h. The solution was evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Elution with dichloromethane-methanol-880ammonia (989:10:1) afforded impure product, followed by the pure title compound (414mg).

Tlc SiO_2(CH_2Cl_2-MeOH-NH_3, 989:10:1)Rf 0.05; detection UV.

(vi) {4-[5-(2-Piperidin-4-yl-(E)-vinyl)-3-(pyrrolidine-1-carbonyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid bis(trifluoroacetate)

4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-(pyrrolidine-1-carbonyl)-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (379mg) was treated with trifluoroacetic acid (8 ml) and after 2h at 23°, the solution was evaporated *in vacuo*. The residue was purified by preparative HPLC using standard conditions, gradient profile 10-90% (ii) in 25 min. The collected eluant , RT 15.8min, was evaporated *in vacuo* to give an oil. This was treated with water

(2 ml) and the precipitate collected to give the title compound (171 mg) as fine white crystals.
Mass spectrum *m/z* 466(MH^+)
Analysis Found:C,51.7; H, 5.6; N, 10.0.
$C_{26}H_{35}N_5O_3.2CHF_3O_2$ requires C, 51.95; H 5.4; N, 10.1%

Example 37
Synthesis of (4-[5-(2-piperidin-4-yl-ethyl)-3-(pyrrolidine-1-carbonyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)
A solution of {4-[5-(2-piperidin-4-yl-(E)-vinyl)-3-(pyrrolidine-1-carbonyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid bis(trifluoroacetate) (90mg) in water (40ml) was added to a pre-hydrogenated suspension of 10% palladium-on-carbon (containing 50% of water, 65mg) in water (10ml) and stirred under hydrogen for 4h. The catalyst was filtered off, washed with water, treated with trifluoroacetic acid (2 drops), and evaporated *in vacuo*. The residue was triturated with ether (10ml) to give the title compound as fine white crystals (63mg).
Mass spectrum m/z 468.2 (MH^+)
Analysis. Found: C, 47.4 ; H, 5.2 ; N, 9.0 ;
$C_{26}H_{37}N_5O_3.3C_2HF_3O_2$ requires C, 47.5 ; H, 5.0 ; N, 8.65 %.

The following compounds were made by methods analogous to those described in Examples 36 and 37.

Example 38
{4-[3-Isopropylcarbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate).
Mass spectrum m/z 454 (MH^+)

Example 39
{4-[3-Isopropylcarbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate.
Mass spectrum. m/z 456 (MH^+).

Example 40

Synthesis of {4-[3-cyano-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid.

(i) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-cyano-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

DMF (0.15ml) was added at -10° under nitrogen to a stirred solution of oxalyl chloride (0.16ml) in acetonitrile (3.5ml). After 15 min, a solution of 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-carbamoyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (350mg) and diisopropylethylamine (0.64ml) in acetonitrile (2ml) was added and stirring continued for 1h. Further oxalyl chloride (0.10ml) was added and stirring continued for 15 min. The dark red solultion was evaporated *in vacuo* and the residue treated with aqueous saturated sodium bicarbonate (25ml). The mixture was extracted with ethyl acetate, and the combined dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography over silica gel. Elution with dichloromethane:ethanol:880 ammonia (989:10:1) afforded the title compound as a cream foam (209mg).
T.l.c. SiO_2 (CH_2Cl_2:EtOH:880NH_3, 978:20:2) Rf 0.16.

(ii) {4-[3-Cyano-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

A solution 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-cyano-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (190mg) in trifluoroacetic acid (8ml) was kept at 23° for 4h and evaporated *in vacuo*. The residue was purified by preparative HPLC using standard conditions gradient profile 10-24% (ii) in 1 min., 24% (ii) isochratic for 11 min. The collected eluant, RT 9.0min, was evaporated *in vacuo* and the residue triturated with ether to give the title compound as fine white crystals (120mg).
Mass spectrum m/z 394 (MH^+).
Analysis Found: C,45.2; H,4.3; N,9.1.
$C_{22}H_{27}N_5O_2.3.1C_2HF_3O_2$ requires C,45.35; H,4.1; N,9.4%.

Example 41

Synthesis of {4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid.

(i) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-hydrazinocarbonyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-5-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-(E)-vinyl]-1H-indazole-3-carboxylic acid methyl ester (0.54g), hydrazine (0.28ml) and THF (5ml) was heated at 100° in an autoclave for 48h. There was some reaction so further hydrazine (1ml, 31.8mmol) was added and heating continued for 2 days. The mixture was evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution with dichloromethane:ethanol:880 ammonia (gradient 978:20:2 to 956:40:4) afforded the title compound as a clear gum (319mg).

Mass spectrum m/z 583 (MH^+)

(ii) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-(5-methyl-[1,3,4]oxadiazol-2-yl)-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-hydrazinocarbonyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (280mg) and triethylorthoacetate (10ml) was stirred at 120° under nitrogen for 20h. The solution was purified by flash chromatography over silica gel eluting with dichloromethane:ethanol:880 ammonia (gradient 989:10:1 to 978:20:2) to give crude product which was further purified by short path chromatography over silica gel to give the title compound as a white foam (92mg).

Mass spectrum m/z 607 (MH^+)

(iii) {4-[3-(5-Methyl-[1,3,4]oxadiazol-2-yl)-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

A solution of 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-(5-methyl-[1,3,4]oxadiazol-2-yl)-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (88mg) in trifluoroacetic acid (3ml) was kept at 23° for 5h. The solution was evaporated *in vacuo* and the residue triturated with ether. The collected solid was dried *in vacuo* to give the title compound as a white solid (110mg).

Mass spectrum m/z 451 (MH^+)

Analysis Found: C,46.6; H,4.7; N,10.9.
$C_{24}H_{30}N_6O_3.2.7C_2HF_3O_2$ requires C,46.6; H,4.35; N,11.1%.

Example 42

Synthesis of {4-[3-morpholin-4-yl methyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid.

(i) 5-Bromo-3-morpholin-4-ylmethyl-1H-indazole

A mixture of 5-bromo-3-chloromethyl-1-H-indazole[9] (0.97 g) and morpholine (0.85 ml) in anhydrous N,N-dimethylformamide (15 ml) was heated at 60° under an atmosphere of nitrogen for 16h. The solvent was removed *in vacuo* and the residue partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organic extracts washed with brine, dried over anhydrous sodium sulphate and concentrated *in vacuo* to yield an orange oil. Purification by flash column chromatography on silica gel eluting with dichloromethane, ethanol ammonia (100:5:1-100:10:1) yielded the title compound as an orange oil (0.729g).

NMR (CDCl3) δ values 10.2 (1H), 8.08 (1H), 7.47 (1H), 7.35 (1H), 3.88 (2H), 3.72 (4H), 2.54 (4H)

REF[9] :Synthetic Communications, 1988, 18, 259.

(ii) 4-(5-Bromo-3-morpholin-4-ylmethyl-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 5-bromo-3-morpholin-4-ylmethyl-1H-indazole (1.89 g), 4-methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester (2.2 g) and potassium carbonate (2.6 g) in anhydrous DMF was heated at 100° under an atmosphere of nitrogen for 26 h. Additional mesylate (2.2g) and potassium carbonate (2.6 g) were added and stirring continued at 100° for 4 h. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over anhydrous sodium sulphate and concentrated *in vacuo* to yield a red oil. Purification by flash column chromatography on silica gel, eluting with dichloromethane, ethanol ammonia (100:1:1 to 100:2:1) yielded the title compound as an orange foaming oil (1.48g).

Mass spectrum m/z 479 (MH+).

(iii) 5-Bromo-3-morpholin-4-ylmethyl-1-piperidin-4-yl-1H-indazole bis(trifluoroacetate)

A solution of 4-(5-bromo-3-morpholin-4-ylmethyl-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (1.47 g) in trifluoroacetic acid/water (9/1, 10 ml) was stirred at 24° for 3 h. The solvent was removed *in vacuo* and the orange oil azeotroped with toluene to yield the crude title compound as a yellow solid. (2.2g)

Mass spectrum m/z 379 (MH+).

(iv) [4-(5-Bromo-3-morpholin-4-ylmethyl-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester

A solution of crude 5-bromo-3-morpholin-4-ylmethyl-1-piperidin-4-yl-1H-indazole bis(trifluoroacetate) (2.2g) and triethylamine (1.7 ml) in dry DMF (15ml) was stirred at 24° under nitrogen for 30 min. tert-Butylbromoacetate (0.5 ml) was added and the solution stirred at 24° for 16 h. Triethylamine (0.34 ml) and tert-butylbromoacetate (0.1 ml) were added and stirring continued at 24° for 4 h. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic extracts washed with brine, dried over anhydrous sodium sulphate and concentrated *in vacuo* to yield a red oil. Purification by flash column chromatography on silica gel eluting with dichloromethane, ethanol ammonia (100:2:1) yielded the title compound as an oil (0.853g).

NMR ($CDCl_3$) δ values 8.01 (1H), 7.4 (1H), 7.35 (1H), 4.38 (1H), 3.84 d (2H, s, CH_2),.3.72 (4H), 3.22 (2H), 3.12 (2H), 2.55-2.33 (8H), 1.98 (2H), 1.50 (9H).

(v) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-morpholin-4-ylmethyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A mixture of [4-(5-bromo-3-morpholin-4-ylmethyl-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester (853 mg), palladium acetate (39 mg), tri(ortho-tolyl)phosphine (90 mg), 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester (401 mg) and triethylamine (0.725 ml) in dry DMF (5ml) was heated at 110° under nitrogen for 24 h. The solvent was removed *in vacuo* and the mixture partitioned between ethyl acetate and aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate and the combined organic

extracts were dried over sodium sulphate and concentrated *in vacuo* to yield a red gum. Purification by flash column chromatography on silica gel eluting with dichloromethane, ethanol ammonia (100:1:1) yielded the title compound (1.02g). Mass spectrum m/z 625 (MH+)

(vi) {4-[3-Morpholin-4-ylmethyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)

A solution of 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-morpholin-4-ylmethyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (940 mg) in trifluoroacetic acid:water (9:1) was allowed to stand at 24° for 6 h. The solvent was removed *in vacuo* to yield the title compound as a brown oil. Mass spectrum m/z 468 (MH+)

(vii) {4-[3-Morpholin-4-ylmethyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)

{4-[3-Morpholin-4-ylmethyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate) was hydrogenated at 24° over 10% palladium on charcoal (50% paste with water, 0.3 g) in 80:20 water: ethanol (20 ml) for 16 h. The catalyst was filtered off and the solvent evaporated *in vacuo*. Purification by preparative reverse phase hplc (gradient profile 10-60% (ii) in 17min., retention time 9.5min, detection wavelength 254nm) yielded the title compound as a pale grey solid (0.357g).

Mass spectrum m/z 470 (MH+)

Assay Found: C, 45.25; H, 4.9; N, 8.4%.

$C_{26}H_{39}N_5O_3$. 3.6 $C_2HF_3O_2$ requires: C, 45.3; H, 4.9; N 8.0%.

Example 43

Synthesis of (4-{5-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-indazol-1-yl}piperidin-1-yl)-acetic acid.

(i) {4-{5-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1H-indazol-1-yl}-piperidin-1-yl)-acetic acid tert-butyl ester

A mixture of [4-(5-bromo-indazol-1-yl)-piperidin-1-yl]-acetic acid, tert-butyl ester (0.49g), 4-vinyl-1-aza-bicyclo[2.2.2]octane[10] (0.172g), tri-o-tolylphosphine (0.076g), palladium II acetate (0.028g) and triethylamine (0.52ml) in dry dimethylformamide (30ml) was stirred at 125°C under nitrogen for 24h. More

palladium II acetate (0.028g) and tri-o-tolylphosphine (0.076g) were added, and the reaction was stirred for a further 18h. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane and 8% aqueous sodium bicarbonate solution. The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash column chromatography on silica gel eluting with triethylamine:diethyl ether (2:98), followed by triethylamine:ethanol:dichloromethane 10:10:80, gave the title compound as an off-white solid (0.343g).

T.l.c. SiO_2 (Et_3N:EtOH:CH_2Cl_2 1:1:8) Rf = 0.32

REF[10]. E. Ceppi et al., Helv. Chem. Acta, 1974, 57, 2332.

(ii) (4-{5-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-indazol-1-yl}-piperidin-1-yl)-acetic acid tris(trifluoroacetate)

A solution of (4-{5-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1H-indazol-1-yl}-piperidin-1-yl)-acetic acid tert-butyl ester (0.34g) in trifluoroacetic acid (5ml) and water (1ml) was allowed to stand at 20° for 4h. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (gradient profile 10-20% (ii) for 10 min and 20% (ii) isochratic for 8 min) to give the title compound (150mg) as a white solid.

Mass spectrum m/z 395 (MH^+)

Analysis Found: C,47.6; H,5.2; N,7.6.

$C_{23}H_{30}N_4O_2.3CF_3CO_2H$ requires C,47.3; H,4.5; N,7.6.

Similarly prepared were:

Example 44

(4-{6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid methyl ester trifluoroacetate.

Mass spectrum m/z 409 (MH^+)

Example 45

{4-[6-[2-(1-Aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(4-fluoro-benzyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid methyl ester trifluoroacetate.

Mass spectrum m/z 517 [MH^+]

Example 46

Synthesis of {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)

(i) 5-Bromo-2-nitro-2H-indazole

To stirred acetic anhydride (410ml) at -5° was added, dropwise, fuming nitric acid (8.5ml). After 20 min. the solution was cooled to -15° and 5-bromoindazole[11] (7.70g) was added portionwise maintaining the temperature at -15°. The mixture was stirred at -15° for 2h, added to iced water (1l), and vigorously stirred for a further 2h. The solid was collected by filtration and was partitioned between diethyl ether and 5M aqueous sodium hydroxide. The aqueous layer was extracted with diethyl ether and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as an orange solid (7.45g).

Mass spectrum m/z 243 (MH^+)

[11]Ref: C. Dell'Erba et al, Tetrahedron, 1994, 50, 3529.

(ii) 5-Bromo-3-methanesulfonyl-1H-indazole

A mixture of 5-bromo-2-nitro-2H-indazole (3.12g) and sodium methanesulfinate (2.89g) in DMF (20ml) was stirred at 20° for 5h. The mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a yellow solid (1.88g).

Mass spectrum m/z 294 (MNH_4^+)

(iii) 4-(5-Bromo-3-methanesulfonyl-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester

A stirred mixture of 5-bromo-3-methanesulfonyl-1H-indazole (1.20g), 4-methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester[12] (1.58g), potassium carbonate (1.81g) and N,N-dimethylformamide (20ml) was heated at 100° for 18h. The cooled mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate:cyclohexane 1:5 to give the title compound as a cream solid (1.37g).

Mass spectrum m/z 459 (MH^+)

[12]Ref: EP-A-0 560 268 A1

(iv) 5-Bromo-3-methanesulfonyl-1-piperidin-4-yl-1H-indazole

A solution of 4-(5-bromo-3-methanesulfonyl-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (1.36g) in trifluoroacetic acid (10ml) was stirred at 20° for 1.5h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane and 0.5M aqueous sodium hydroxide. The aqueous layer was extracted with dichloromethane and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a cream solid (0.90g).

Mass spectrum m/z 360 (MH^+)

(v) [4-(5-Bromo-3-methanesulfonyl-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester

A mixture of 5-bromo-3-methanesulfonyl-1-piperidin-4-yl-1H-indazole (0.90g), tert-butylbromoacetate (0.390ml) and sodium bicarbonate (0.380g) in N,N-dimethylformamide (15.0ml) was stirred at 20° for 20h. The mixture was concentrated in vacuo and the residue partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane, and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel (Merck 9385), eluting with ethyl acetate-cyclohexane (gradient 1:4 to 1:3) to give the title compound as a cream solid (0.870g).

Mass spectrum m/z 474 (MH^+)

(vi) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-methanesulfonyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A stirred mixture of [4-(5-bromo-3-methanesulfonyl-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester (0.350g), 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester[13] (0.177g), triethylamine (0.320ml), palladium (II) acetate (0.014g), tri-o-tolylphosphine (0.037g) and N,N-dimethylformamide (2.50ml), was heated at 110° under nitrogen for 16h. The cooled mixture was concentrated *in vacuo* and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel (Merck 9385), eluting with

dichloromethane :ethanol:880 ammonia (80:18:2) to give the title compound as a white solid (0.270g).
Mass spectrum m/z 603 (MH^+)
REF[13]: PCT/EP95/05043

(vii) {4-[3-Methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate salt

4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-methanesulfonyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (0.270g) was dissolved in trifluoroacetic acid (10ml) and the mixture was stirred at 20° for 5 h. The mixture was concentrated *in vacuo*, and the residue purified by trituration with diethyl ether. The resulting solid was collected by filtration and dried *in vacuo* to afford the title compound as a cream solid (0.170g).
Mass spectrum m/z 447 (MH^+)
Analysis: Found : C, 42.0; H, 3.9; N, 6.8; S, 3.9
$C_{22}H_{30}N_4O_4S.3.2CF_3CO_2H$ requires: C, 42.0; H, 4.1; N, 6.9; S, 3.95%

Example 47

Synthesis of {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate salt.

Method A

{4-[3-Methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate) (0.782g) was hydrogenated at room temperature and pressure over 10% palladium on carbon (50% paste, 0.20g) in water:ethanol 70:30 for 6h. The catalyst was filtered off and the solvent evaporated *in vacuo* to give a yellow oil (0.577g). Purification by preparative HPLC (gradient profile 10-75% (ii) in 20min, detection 250nM, RT 10.3min) and trituration of the resulting gum with dry ether gave the title compound as a white solid (0.180g).
Mass spectrum m/z 449 (MH^+)
Analysis Found: C, 44.6; H, 5.2; N 7.8; S, 4.3.
C22H32N4O4S.2.4CF_3COOH requires: C, 44.6; H 4.8; N 7.8; S,4.4.

Method B

(a) 4-Bromo-(2-methylthiomethyl)aniline

Dimethylsulfide (105 ml) was added dropwise to a stirred solution of N-chlorosuccinimide (139.7 g) in dichloromethane (3750 ml) at 0 to -5 °C and the resulting suspension cooled to -20°C. To this was added dropwise a solution of 4-bromoaniline (150.0 g) in dichloromethane (300 ml), the suspension stirred at -20°C for 0.5h and the reaction mixture diluted with triethylamine (292 ml). The reaction mixture was stirred at ambient temperature for 58h. washed with water, 2N hydrochloric acid, 8% w/w aqueous sodium bicarbonate. dried ($MgSO_4$) and evaporated in vacuo to give the title compound as a pale yellow solid (162.0 g).
Mass spectrum m/z 232.9 (MH^+)

(b) 5-Bromo-3-methylsulfinyl-1H-indazole

A solution of sodium nitrite (48.4 g) in water (100 ml) was added dropwise to a stirred solution of 4-bromo-(2-methylthiomethyl)aniline (163.0 g) and fluoboric acid (230 ml, 48%w/w aqueous solution) in water (815 ml) at 10-15 °C. The resulting yellow suspension was stirred at ambient temperature for 1h, the solid isolated by filtration, the solid washed with water and diethylether and finally suspended in chloroform (4000 ml). The stirred suspension was treated with potassium acetate (138.0 g) and 18-Crown-6 (9.30 g) and stirred at ambient temperature for 2h. The reaction mixture was filtered and the filtrate washed with 2N sodium hydroxide, dried ($MgSO_4$) and evaporated in vacuo to give the title compound as a pale yellow solid (147.7 g).
Mass spectrum m/z 243.9 (MH^+)

(c) 5-Bromo-3-methylsulfonyl-1H-indazole

Oxone™ (182.2 g) was added portionwise to a stirred suspension of 5-bromo-3-methylsulfinyl-1H-indazole (36.0 g) in methanol (450 ml) and water(135 ml). The reaction mixture was stirred at ambient temperature for 3h, concentrated in vacuo and the resulting oil partioned between ethyl acetate and water. The biphasic mixture was separated, the aqueous phase extracted with ethyl acetate, the combined organic extracts were washed with 8 %w/w aqueous sodium bicarbonate and water, dried ($MgSO_4$) and evaporated in vacuo to give the title compound as a off-white solid (38.8 g).
Mass spectrum m/z 293.9 (MNH_4^+)

(d) 4-[3-Methanesulfonyl-5-{1-(1-tert-butoxycarbonylmethyl-2-piperidin-

4-yl-ethyl)}-1H-indazol-1yl]-1-piperidine acetic acid tert-butylester

A solution of 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-methanesulfonyl-1H-indazol-5-yl]-(E)-vinyl}-1-piperidine acetic acid tert-butyl ester (77.0 g) in ethanol (760 ml) was added to a pre-hydrogenated suspension of 10% Pd/C (115.5g) in ethanol (77 ml) and water (19 ml) and the resulting stirred suspension hydrogenated at ambient temperature for 26h. The reaction was filtered through hyflo, the residue washed with ethanol and the combined filtrate evaporated in vacuo to give a pale green oil which was purified by Biotage chromatography, eluting with ethyl acetate : cyclohexane (1:1), to give the title compound as a gum-solid (46.8 g).

Mass spectrum m/z 605.3 (MH^+)

(e) 4-[3-Methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-1H-indazol-1-yl]-1-piperidine acetic acid dihydrochloride

A solution of 4-[3-Methanesulfonyl-5-{1-(1-tert-butoxycarbonylmethyl-2-piperidin-4-yl-ethyl)}-1H-indazol-1yl]-1-piperidine acetic acid tert-butylester (25.0 g) in trifluoroacetic acid (250 ml) was stirred at ambient temperature for 4h. The reaction mixture was evaporated in vacuo and the residue purified by preparative HPLC, eluting with water : acetonitrile : trifluoroacetic acid (gradient 90:10:0.1 to 25:75:0, 20 min, detection 260nm, RT 13 min), to give a white solid which was dissolved in 2N hydrochloric acid and evaporated in vacuo to give the a white solid. The hydrochloric acid procedure was repeated twice. The white solid was trituated with acetone (100 ml) and the suspension evaporated in vacuo. The solid was again trituated with acetone (100 ml), the suspension stirred at ambient temperature for 0.5h and the solid isolated by filtration, washed with acetone and dried in vacuo at 45°C to constant weight to give the title compound as a white crystalline solid (10.03 g).

Analysis found: C, 46.9; H, 6.8; N, 9.9

$C_{22}H_{32}N_4O_4$ S.2HCl.2H2O requires: C, 47.3; H, 6.8; N, 10.0 %

Example 48

Synthesis of {4-[3-Carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

(a) 5-Bromo-1-(1-tert-butoxycarbonyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester

5-Bromo-1H-indazole-3-carboxylic acid[14], methyl ester (35.8g) in dry THF (400ml) containing 4-methanesulphonyloxy-piperidine-1-carboxylic acid tert-butyl ester[12] (40.9g, 153mmol) was treated with potassium t-butoxide (15.75g, 140mmol) and stirred at reflux under nitrogen for 24h. When cool, the mixture was evaporated *in vacuo* and the residue treated with aqueous saturated ammonium chloride (400ml). The mixture was extracted with ethyl acetate and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* onto silica gel. The resultant silica was applied as a plug to a flash column of silica gel, eluting with cyclohexane:ethyl acetate (gradient 19:1 to 3:1) to give firstly an isomer followed by the title product (22.8g).

T.l.c. SiO_2 (cyclohexane:EtOAc, 7:3), Rf 0.29.

REF [14] G.A. Bistrocchi et al., Farmaco. Ed. Sci., 1981, 36, 315.

(b) 5-Bromo-1-piperidin-4-yl-1H-indazole-3-carboxylic acid methyl ester bis(trifluoroacetate)

Trifluoroacetic acid (100ml) was added to 5-bromo-1-(1-tert-butoxycarbonyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester (22.75g) at 23° during 1 min. After 1h, the mixture was evaporated *in vacuo* and the co-evaporated with dichloromethane to give the title product (28.05g) as a light yellow solid.

T.l.c. SiO_2 (CH_2Cl_2:EtOH:880NH_3, 89:10:1), Rf 0.18.

(c) 5-Bromo-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester

A solution of 5-bromo-1-piperidin-4-yl-1H-indazole-3-carboxylic acid methyl ester bis(trifluoroacetate) (28.05g) and tert-butylbromoacetate (7.3ml) in DMF (500ml) was treated with diisopropylethylamine (25.9ml) under nitrogen with stirring at 23° and kept for 4 days. Further tert-butylbromoacetate (1.4ml), followed by diisoproplyethylamine (5.0ml) were added and stirring continued for 2h. The mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (400ml), and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue crystallised from ethyl acetate to give the title product (13.43g).

T.l.c. SiO_2 (Cyclohexane:EtOAc, 7:3) Rf 0.17.

(d) 1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-5-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-(E)-vinyl]-1H-indazole-3-carboxylic acid methyl ester

A mixture of 5-bromo-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester (13.43g), 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester(6.90g), palladium (II) acetate (666mg), tri-o-tolylphosphine (1.81g), triethylamine (12.4ml, 89.1mmol), and DMF (200ml) was stirred at 120° under nitrogen for 15h. When cool, the mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (200ml), and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel . Gradient elution with dichloromethane:ethanol:880 ammonia (gradient 989:10:1 to 978:20:2) to afford the title compound as a light orange foam (8.94g).

T.l.c. SiO_2 (CH_2Cl_2:EtOH:880NH_3, 978:20:2) Rf 0.14.

(e) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-carbamoyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-5-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-(E)-vinyl]-1H-indazole-3-carboxylic acid methyl ester (600mg) in methanol (20ml) saturated with ammonia was heated at 80° for 50h. The cooled solution was evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution with dichloromethane:ethanol:0.88 ammonia (gradient 989:10:1 to 967:30:3) afforded the title product as a white foam (373mg).

T.l.c. SiO_2 (CH_2Cl_2:EtOH:880NH_3, 978:20:2) Rf 0.08.

(f) {4-[3-Carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

A solution of 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-carbamoyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (292mg) in trifluoroacetic acid (6ml) was kept at 23° for 2h. The solution was evaporated *in vacuo*, co-evaporated with water (3ml), and triturated with diethyl ether to give the title product as a white solid (311mg).

Mass spectrum *m/z* 412 (MH^+).

Analysis Found: C,45.0; H,4.8; N,9.4.

$C_{22}H_{29}N_5O_3.2.8CF_3CO_2H$ requires C,45.4; H,4.4; N,9.6%.

Example 49

Synthesis of {4-[3-Carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

Method A

A solution of {4-[3-carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid trifluoroacetate (100mg) in water (40ml) was added to a suspension of prehydrogenated 10% palladium on activated carbon (70mg) in water (10ml) and stirred under hydrogen for 4h. The catalyst was filtered off, washed, and the filtrate treated with trifluoroacetic acid (2 drops). The solution was evaporated *in vacuo*, and the residue was triturated with ether to give the title product as fine white crystals (74mg).

Mass spectrum. m/z 414.1 (MH^+)

Analytical HPLC RT 9.2 min.

Analysis Found: C, 45.7 ; H,.4.9 ; N, 9.9.

$C_{22}H_{31}N_5O_3$,2.65 CF_3CO_2H requires C, 45.8; H, 4.7 ; N, 9.8 %.

Method B

(a) 5-bromo-3-formyl-1H-indazole

A solution of 5-bromoindole (100g) and sodium nitrite (350g) in 1,4-dioxane (3.5L) and water (18vol.) was acidified to pH 2.5 by the steady addition of 3N hydrochloric acid (18L) over 0.5h at 20-25°. The mixture was stirred for 0.75h and then extracted with ethyl acetate. The combined organic extracts were diluted with ethyl acetate (1L) and washed with water. The combined water washes were extracted with ethyl acetate. The organic layer was washed with water, combined with the main organic extract and evaporated to give a dark black-brown solid. This solid was triturated with ethyl acetate (200ml) for 1h, filtered and the filter cake washed with ethyl acetate and dried to give the title compound as a red-brown solid (60.8g).

Mass spectrum m/z 223, 225 $[M-H^+]^-$

(b) 5-Bromo-3-cyano-1H- indazole

A suspension of 5-bromo-3-formyl-1H-indazole (143g) was heated to 65-70° in a solution of hydroxylamine-O-sulfonic acid (93.4) in water (1.4L) for 16h. The mixture was cooled to 20° over 1h, filtered and the filter cake washed with water

and dried at 45°C to give a solid (146g). This solid was heated at reflux in toluene (3.65L) for 1h and filtered at 90°C. The filtrate was re-heated to give a solution, stirred and cooled to 10°. The suspension is filtered, the filter cake washed with toluene and dried to give the title compound as a pale brown solid (111g).

Mass spectrum m/z 220, 222 [M-H$^+$]$^-$

(c) 4-(5-Bromo-3-cyano-IH-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester

A suspension of 5-bromo-3-cyano-1H-indazole (111g), 1-tert-butoxycarbonyl-4-methylsulphonyl-piperidine (168g) and potassium carbonate (193g) in DMF (1.1L) was heated at 105-110° for 6h, evaporated to dryness and the orange residue partitioned between dichloromethane and water. The aqueous phase was re-extracted with dichloromethane, the combined organics washed with water and evaporated to an orange residue (130g). This residue was triturated with a mixture of cyclohexane and ethyl acetate (6:1, 1.04L) for 1h and filtered. The filter cake was washed with a mixture of cyclohexane and ethyl acetate and dried to give the title compound as a pale yellow powder (125g).

Mass spectrum m/z 405, 407 [MH$^+$]

(d) 5-Bromo-1-pipidin-4-yl-1H-indazole-3-carboxamide

4-(5-bromo-3-cyano-IH-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (62g) was added portionwise over 1h at 20-30° to conc. sulfuric acid (620g) and the suspension stirred for 2h. The mixture was poured onto ice (1.24kg), basified to pH12 with 5N sodium hydroxide (2.44L) at 20-30° over 1.5h, diluted with water (300ml) and filtered. The filter cake was washed with water and dried to give the title compound as an off-white solid (51.5g).

Mass spectrum m/z 323, 325 [MH$^+$]

(e) 4-(5-Bromo-3-aminocarbonyl-1H-indazol-1-yl)-1-piperidine acetic acid tert-butyl ester

tert-Butyl bromoacetate (60.4g) was cautiously added to a solution of 5-bromo-1-pipidin-4-yl-1H-indazole-3-carboxamide (100g) and triethylamine (43.3ml) in DMF (1L) at 20-30° and stirred for 2h. Water (1.5L) was added dropwise over 1h to the mixture at <25°, the suspension stirred for 1h and filtered. The filter

cake was washed with water and dried to give the title compound as a pale yellow solid (121g).
Mass spectrum m/z 437, 439 [MH^+]

(f) 4-{2-[3-Aminocarbonyl-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester.
A mixture of 4-(5-Bromo-3-aminocarbonyl-1H-indazol-1-yl)-1-piperidine acetic acid tert-butyl ester (120g), 4-(E)-vinyl-piperidine-1-carboxylic acid tert-butyl ester (60.8g), triethylamine (114.6ml), tri-ortho-tolylphosphine (16.7g), palladium acetate (6.2g) and harborlite J2 filter aid (60g) was heated at 105-110° in DMF (2.4L) for 14h. The mixture was cooled to *ca.*35°, charcoal (30g) was added and the mixture stirred for 1h at *ca.*35° before cooling to ambient temperature. The mixture was filtered and the filter pad washed with N, N-dimethylformamide and cyclohexane. The combined filtrate was diluted with water (240ml), the phases separated and the N, N-dimethylformamide/water extract washed with cyclohexane and concentrated to a red gum. The gum was stirred in water (600ml) for 1h, further water (1.8L) was added and the suspension stirred for 0.5h and filtered. The filter cake was washed with water and
dried to give the title compound (153g) as a yellow-orange solid.
Mass spectrum m/z 568 [MH^+]

(g) 4-{2-[3-Aminocarbonyl-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-5-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester.
10% Palladium-carbon catalyst (73.5g) was added to a solution of 4-{2-[3-Aminocarbonyl-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (147g) in tetrahydrofuran (2.94L) and stirred under a hydrogen atmosphere at ambient temperature for 5h. A second charge of 10% palladium-carbon catalyst (73.5g) and tetrahydrofuran (200ml) was added and the suspension stirred under hydrogen for a further 18h before a third charge of catalyst (73.5g) and tetrahydrofuran (200ml) was added and the suspension stirred under hydrogen for another 20h. The mixture was filtered, washed with tetrahydrofuran and evaporated to a thick black oil. This oil was purified by Biotage chromatography over silica gel eluting with ethyl acetate-cyclohexane (1:1) and then ethyl acetate to give the title compound as white crystals (32.65g).

Mass spectrum m/z 570 [MH^+]

(h) {4-[3-Carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

4-{2-[3-Aminocarbonyl-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-5-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester (32.65g) was added in two equal portions to trifluoroacetic acid (330ml) and the solution stirred at ambient temperature for 3h. The mixture was concentrated to 100g weight and purified by preparative HPLC (Kromsil C8, 10µm, reverse phase), eluting with water-acetonitrile-trifluoroacetic acid, 90:10:0.1%v/v (A) and water-acetonitrile, 25:75 (B) to give a white solid (26g). The solid (23.6g) was dissolved in HPLC grade water (60ml) and adjusted to pH10 with 880 ammonia solution (20ml) added at 20-30° over 0.5h. The milky-white suspension was stirred at 20° for 1.5h and filtered. The filter cake was washed with water with sucking under vacuum for 10min between each wash, dried at 40° for 18h and left to equilibrate under ambient conditions for 4h to give the title compound as a white powder (12.05g).

Mass spectrum m/z 414 [MH^+]

Example 50

Synthesis of {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid.

(a) 1-[4-(2,4-Dibromo-benzoyl)-piperidin-1-yl]-ethanone

1,3-Dibromobenzene (65ml) was added to a stirred mixture of 1-acetyl-piperidine-4-carbonyl chloride hydrochloride[15] (21.8g) and aluminium (III) chloride (34.5g) and the mixture heated at 95-100° for 1.5h. When cool, the mixture was poured into a mixture of ice-water (50ml) and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel (Merck 9385). Gradient elution with ether - ethanol (gradient 99:1 to 90: 10) afforded the title compound as an orange oil (16.7g).

T.l.c. SiO_2 (Et_2O - EtOH, 9:1) Rf = 0.23

REF [15] EP-A-0 428 437

(b) (2,4-Dibromo-phenyl)-piperidin-4-yl-methanone hydrochloride

A stirred mixture of 1-[4-(2,4-dibromo-benzoyl)-piperidin-1-yl]-ethanone (11.00g) and aqueous 5M hydrochloric acid (60ml) was heated under reflux under nitrogen for 7h. The mixture was evaporated *in vacuo* to give the title compound as a white solid (10.8g).

T.l.c. SiO_2 (CH_2Cl_2-EtOH-880NH_3, 89:10:1) Rf = 0.17

(c) (2,4-Dibromo-phenyl)-piperidin-4-yl-methylene-hydrazine

A stirred solution of (2,4-dibromo-phenyl)-piperidin-4-yl-methanone hydrochloride (7.04g), hydrazine (6.0ml), and ethanol (150ml) was heated under reflux under nitrogen for 16h. The cooled solution was evaporated *in vacuo*, treated with aqueous 1M sodium carbonate (50ml), extracted with ether, and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography (Merck 9385) eluting with dichloromethane-ethanol-880 ammonia (gradient 89:10:1 to 835:150:15) to give the title compound as a cream solid (5.71g).

T.l.c. SiO_2 (CH_2Cl_2-EtOH-880 NH_3, 78:20:2) Rf = 0.13 (minor) and Rf = 0.16 (major)

(d) 6-Bromo-3-piperidin-4-yl-1H-indazole hydrochloride

A stirred mixture of (2,4-dibromo-phenyl)-piperidin-4-yl-methylene-hydrazine (5.64g), sodium hydride (1.25g, 60% dispersion in oil), and dry DMF (150ml) was heated at 105° under nitrogen for 6.5h. Further sodium hydride (200mg) was added and heating continued for 2h. The mixture was evaporated *in vacuo* acidified to pH 1 by the addition of aqueous 2M hydrochloric acid, and then basified to pH 8 by the addition of aqueous 1M sodium carbonate. The mixture was extracted with ether, and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography (Merck 9385), eluting with dichloromethane - ethanol - 880 ammonia (gradient 89:10:1 to 78:20:2) to give the title compound as a cream-yellow solid (2.50g).

T.l.c. SiO_2 (CH_2Cl_2-EtOH-880NH_3, 78:20:2) Rf = 0.6

(e) [4-(6-Bromo-1H-indazol-3-yl)-piperidin-1-yl]-acetic acid tert-butyl ester

A mixture of 6-bromo-3-piperidin-4-yl-1H-indazole hydrochloride (500mg), tert-butyl bromoacetate (0.29ml), sodium bicarbonate (150mg, 1.87mmol), and DMF

(10ml) was stirred at 23° under nitrogen for 18h. The mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (25ml), and extracted with ethyl acetate (50ml). The dried (Na_2SO_4) organic layer was evaporated *in vacuo* onto silica gel (Merck 7734). Purification by flash chromatography (Merck 9385), eluting with dichloromethane - ethanol - 880 ammonia (gradient 967:30:3 to 945:50:5) afforded the title compound as fine white crystals (347mg).

T.l.c. SiO_2 (CH_2Cl_2-EtOH-880 NH_3, 945:50:5) Rf = 0.27

(f) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A mixture of [4-(6-bromo-1H-indazol-3-yl)-piperidin-1-yl]-acetic acid tert butyl ester (1.34g), 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester (0.75g), triethylamine (1.4ml), palladium (ii) acetate (0.050g) and tri(*o*-tolyl)phosphine (0.210g) in DMF (60ml) was stirred at 120° under nitrogen for 16h. The mixture was evaporated *in vacuo* and purified by flash chromatography (Merck 9385), eluant ethyl acetate: cyclohexane: triethylamine (50:50:2 to 100:0:2), to give the title compound as a yellow solid (1.18g).

T.l.c. SiO_2 (CH_2Cl_2 : EtOH: 880 NH_3 95: 5: 0.5) Rf = 0.32

(g) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1-methanesulfonyl-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (0.211g) in DMF (10ml) was treated with sodium hydride (60% dispersion in oil, 0.019g) and stirred for 0.5h at 23°C under nitrogen. Methanesulphonyl chloride (0.03ml) was added and the mixture stirred for a further 40h. The solvent was evaporated *in vacuo* and the residue was partitioned between water (20ml) and ethyl acetate. The extracts were dried (Na_2SO_4), evaporated *in vacuo*, and purified by flash chromatography on silica gel, eluant cyclohexane:ether:triethylamine 50:50:2, to give the title compound as a colourless gum (0.141g).

Mass spectrum m/z 603 (MH^+).

(h) {4-[1-Methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1-methanesulfonyl-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (0.138g) was treated with trifluoroacetic acid (3ml) and stirred at 22°C for 2h. The solvent was evaporated *in vacuo*, and the residue was purified by preparative HPLC (gradient profile 20-70% (ii) in 18 min, Rf 12.5min). Trituration with ether to give the title compound as a white crystalline solid (0.114g).

Mass spectrum m/z 447.2 (MH^+)

Analysis Found: C,44.5; H,4.7; N,7.7.

$C_{22}H_{30}N_4O_4S.2.4C_2HF_3O_2$ requires C,44.7; H,4.5; N,7.8%.

Example 51

Synthesis of {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid .

Method A

A solution of {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate (690 mg) in water (90 ml) was added to a stirred suspension of 10% palladium on carbon (600 mg) in water (30 ml) and the mixture stirred at 23° under nitrogen for 6h. The catalyst was filtered off and the filtrate evaporated *in vacuo* to give title compound as fine white crystals (420 mg).

Mass spectrum m/z 449 (MH^+)

Analysis. Found: C, 42.6; H, 4.9; N, 7.2.

$C_{22}H_{32}N_4O_4S.3C_2HF_3O_2.0.3C_4H_{10}O$ requires C, 42.4; H, 4.6; N, 6.8%.

Method B

(a) 4-{2-[1-Methanesulfonyl-3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperidine-1-acetic acid tert-butyl ester

Methanesulphonyl chloride (7.6 ml) was added dropwise to a stirred solution of 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperidine-1-acetic acid tert-butyl ester (40.1 g), and 4-*N,N*-dimethylaminopyridine (0.96 g) in pyridine (280 ml) at ambient temperature. The resulting brown solution was stirred at ambient temperature for 18h, diluted with water (400 ml) and extracted with dichloromethane (400 ml). The combined organic extracts were evaporated in vacuo, the brown residue diluted with ethanol (400 ml) and evaporated in vacuo to give a brown oil. The oil was

triturated with ethanol (400 ml) and evaporated in-vacuo to *ca* 200 ml to give a suspension. The resulting solid was isolated by filtration, washed with ethanol and dried in vacuo at 45°C to give the title compound as an off-white solid (37.6 g).

Mass spectrum m/z 605 (MH^+)

(b) 4-[1-Methanesulfonyl-3-(2-piperidin-4-yl-ethyl)-1H-indazol-6-yl]-piperidine-1-acetic acid

A solution of 4-{2-[1-methanesulfonyl-3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperidine-1-acetic acid tert-butyl ester (20 g) in 5N hydrochloric acid (200 ml) was stirred at ambient temperature for 5h. The reaction mixture was neutralised with saturated potassium carbonate (300 ml) and extracted with isopropanol. The combined organic extracts were evaporated in vacuo to give an oil which was diluted with ethanol (300 ml) and concentrated by rotary evaporation to give a white solid. The off-white solid was purified by flash chromatography (Merck 9385) eluting with ethanol : dichloromethane: 0.88 ammonia (gradient: 15:3:1 to 15:3:1.5) afforded the title compound as a white solid (10.1 g).

Analysis found: C,56.3; H,7.7; N,11.0 %

($C_{22}H_{32}N_4O_4S$. 0.80 H_2O. 0.83 C_2H_6O) x 0.984 requires:C,55.8; H,7.6; N,11.1 %

Example 52 - Tablets

a)	Compound of the invention	5.0mg
	Lactose	95.0mg
	Microcrystalline Cellulose	90.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	2.0mg
	Compression weight	200.0mg

The compound of the invention, microcrystalline cellulose, lactose and cross-linked polyvinylpyrrolidone are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron

sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

b)	Compound of the invention	5.0mg
	Lactose	165.0mg
	Pregelatinised Starch	20.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	2.0mg
	Compression weight	200.0mg

The compound of the invention, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Example 53 - Capsules

a)	Compound of the invention	5.0mg
	Pregelatinised Starch	193.0mg
	Magnesium Stearate	2.0mg
	Fill weight	200.0mg

The compound of the invention and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate, (meshed through a 250 micron sieve). The blend is filled into hard gelatine capsules of a suitable size.

b)	Compound of the invention	5.0mg
	Lactose	177.0mg
	Polyvinylpyrrolidone	8.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	2.0mg
	Fill weight	200.0mg

The compound of the invention and lactose are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried and

milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granules. The resultant blend is filled into hard gelatine capsules of a suitable size.

Example 54 - Syrup

a)	Compound of the invention	5.0mg
	Hydroxypropyl Methylcellulose	45.0mg
	Propyl Hydroxybenzoate	1.5mg
	Butyl Hydroxybenzoate	0.75mg
	Saccharin Sodium	5.0mg
	Sorbitol Solution	1.0ml
	Suitable Buffers	qs
	Suitable flavours	qs
	Purified Water to	10.ml

The hydroxypropyl methylcellulose is dispersed in a portion of hot purified water together with the hydroxybenzoates and the solution is allowed to cool to ambient temperature. The saccharin sodium flavours and sorbitol solution are added to the bulk solution. The compound of the invention is dissolved in a portion of the remaining water and added to the bulk solution. Suitable buffers may be added to control the pH in the region of maximum stability. The solution is made up to volume, filtered and filled into suitable containers.

Example 55 - Injection Formulation

	% w/v
Compound of the invention	1.00
Water for injections B.P. to	100.00

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included. The solution is clarified, made up to final volume with water and the

pH remeasured and adjusted if necessary, to provide 10mg/ml of the compound of formula (I).

The solution may be packaged for injection, for example by filling and sealing in ampoules, vials or syringes. The ampoules, vials or syringes may be aseptically filled (e.g. the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions) and/or terminally sterilised (e.g. by heating in an autoclave using one of the acceptable cycles). The solution may be packed under an inert atmosphere of nitrogen.

Preferably the solution is filled into ampoules, sealed by fusion of the glass and terminally sterilised.

Further sterile formulations are prepared in a similar manner containing 0.5, 2.0 and 5% w/v of the compound of formula (I), so as to provide respectively 5, 20 and 50mg/ml of the compound of formula (I).

Biological Data

1. Human Washed Platelets Assay

Inhibition of platelet aggregation by compounds of the invention was determined according to the following procedure. Citrated whole blood (1 part 3.8% w/v trisodium citrate; 9 parts blood) was obtained from human volunteers, free of medication for at least 10 days prior to donation. The blood was treated with aspirin (0.1mM) and prostacyclin (0.06μM) prior to centrifugation (1400g, 4 minutes, 20°C). The supernatant platelet-rich plasma (PRP) was isolated and further centrifuged (1400g, 10 minutes, 20°C) to sediment the platelets. The supernatant was discarded and the platelet pellet resuspended into a physiological salt solution (HEPES 5mM, $NaHCO_3$ 12mM, NaCl 140mM, KH_2PO_4 0.74mM, D-Glucose 5.6mM and KCl 2.82mM) adjusted to pH 6.4. This platelet suspension was centrifuged (1400g, 8 minutes, 20°C) and the resultant platelet pellet was resuspended into the physiological salt solution adjusted to pH 7.4. The resultant washed-platelet preparation was diluted to give a final platelet count of $3x10^8$/l. Purified human fibrinogen (Knight, L.C. *et al.*, 1981 Thromb. Haemostasis, 46, (3), 593-596), Ca^{2+} and Mg^{2+} were added back to the washed platelet preparation to give final concentrations of 0.5mg/ml, 1mM and

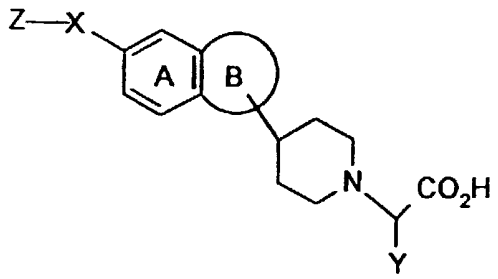
0.5mM respectively. Platelet aggregation was quantified using a turbidometric method. Test compounds were incubated with the washed platelets (37°C) for 5 minutes prior to the addition of 1μM of the platelet aggregatory agonist U-46619 (a stable thromboxane A_2-mimetic). The inhibitory potency of the test compounds was expressed as an IC_{50} value, which is defined as the concentration of the compound required to inhibit platelet aggregation by 50%. The following IC_{50} values were obtained for compounds of the invention:

Table 1

Example no.	IC_{50} (nm)
46	100
47	53
48	<100
49	<100
50	<100
51	<100

CLAIMS

1. A compound of formula (I)



(I)

or a salt, solvate, or physiologically functional derivative thereof, in which:
X is CH_2-CH_2 , CH=CH, or C≡C;

Y is hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, aryl, hetaryl, arylC_{1-4}alkyl, or hetarylC_{1-4}alkyl, wherein

the aryl and hetaryl groups are optionally substituted by halo, nitro, C_{1-6} alkyl, C_{1-6}haloalkyl, hydroxy, C_{1-6} alkoxy, cyano, $-C(O)_nR^1$, $-NR^1S(O)_nR^2$, $-C(O)NR^1R^2$, or $-NR^1R^2$, wherein

R^1 and R^2 are independently selected from hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, and n is 1, or 2;

Z is piperidinyl, piperazinyl, or quinuclidinyl;

ring B is a 5- or 6- membered aromatic heterocycle fused to ring A and is optionally substituted by a group -L-R° wherein:

L is a bond, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $S(O)_n$, $C(O)_n$, or $CONR^3$, wherein

n is 1, or 2, and R^3 is selected from hydrogen, C_{1-4}alkyl, and C_{1-4}haloalkyl; and

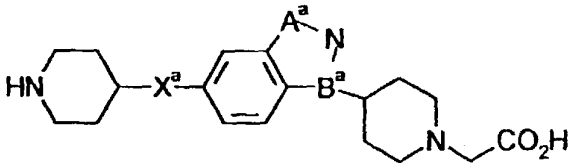
R° is C_{1-6} alkyl, C_{4-7}cycloalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkoxy, cyano,

$-NR^4R^5$, aryl or hetaryl, wherein

R^4 and R^5 are independently selected from hydrogen, C_{1-6} alkyl and C_{1-6} haloalkyl, or together with the nitrogen to which they are bonded form a piperidinyl, morpholino, or pyrolidinyl group, and

the aryl and hetaryl groups are optionally substituted by halo, nitro, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, cyano, $-C(O)NR^6R^7$ or $-NR^6R^7$ wherein R^6 and R^7 are as defined for R^4 and R^5 above,

provided that the compound is not of formula (a)



(a)

or a pharmaceutically acceptable derivative thereof, in which:
X^a is either CH_2-CH_2 or CH=CH; and

either A^a is $-\overset{Y^a}{\underset{|}{N}}-$ and B^a is –C=,
or A^a is –CH= and B^a is –N–, wherein
Y^a is hydrogen or phenylmethyl wherein the phenyl group is optionally substituted by one or more halogen atoms (where halogen represents fluorine, chlorine, bromine or iodine).

2. A compound according to claim 1 with the further proviso that the compound is not selected from:
(a) {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid, {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(Z)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid, {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid ; and/or
(b) {4-[3-carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid, {4-[3-carbamoyl-5-(2-piperidin-4-yl-(Z)-vinyl)-indazol-1-yl]-

piperidin-1-yl}-acetic acid, {4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid; and/or

(c) {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid, {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(Z)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid, {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid:

or a salt, solvate or physiologically functional derivative thereof.

3. {4-[1-(4-carbamoyl-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-carbamoyl-benzyl)-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-fluoro-benzenesulfonyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]piperidin-1-yl}-acetic acid;
(4-{1-[2-(4-fluoro-phenyl)-ethyl]-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid;
[4-[1-(4-nitro-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl]acetic acid;
{4-[1-cyclopentylmethyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-methyl-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-pentyloxy-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-bromo-benzoyl-carbonyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-dimethylamino-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-hydroxy-benzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-cyano-phenyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(3,4-dichloro-phenylcarbamoyl)-6-(2-piperidin-4-yl)-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;

{4-[6-(2-piperidin-4-yl-(E)-vinyl)-1-(2,2,2-trifluoro-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-methylcarbamoyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-carbamoyl-benzyl)-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[6-(2-piperidin-4-yl-(Z)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-pentyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
(4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid;
(4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(3-cyclohexyl-propyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid;
4-[6-[2(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(4-fluoro-benzyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
(4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-1-(4-tert-butyl-benzenesulfonyl)-1H-indazol-3-yl}-piperidin-1-yl)-acetic acid;
{4-[6-(2-piperazin-1-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-fluoro-benzyl)-6-(2-piperazin-1-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
(4-{6-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-(4-chloro-phenyl)-acetic acid;
{4-[6-(2-piperidin-4-yl-(E)-vinyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[6-(2-piperidin-4-yl-ethyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[6-(2-piperazin-1-yl-ethyl)-benzo[d]isoxazol-3-yl]-piperidin-1-yl-acetic acid;
[4-[3-methoxy-5-5(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-methoxy-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-(E)-vinyl)-3-pyrazol-1-yl-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-(E)-vinyl)-3-pyrrolidin-1-yl-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-Morpholin-4-yl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;

{4-[5-(2-piperidin-4-yl-(E)-vinyl)-3-(pyrrolidine-1-carbonyl)-indazol-1-yl]piperidin-1-yl}acetic acid;
(4-[5-(2-piperidin-4-yl-ethyl)-3-(pyrrolidine-1-carbonyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid ;
{4-[3-isopropylcarbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-isopropylcarbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-cyano-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid
{4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-morpholin-4-yl methyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
(4-{5-[2-(1-aza-bicyclo[2.2.2]oct-4-yl)-(E)-vinyl]-indazol-1-yl}piperidin-1-yl)-acetic acid;
and salts, solvates, and physiologically functional derivatives thereof.

4. {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid;
{4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid ;
and salts, solvates, and physiologically functional derivatives thereof.

5. {4-[3-carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
and salts, solvates, and physiologically functional derivatives thereof.

6. {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
and salts, solvates, and physiologically functional derivatives thereof.

7. The hydrochloride salt of a compound according to any one of claims 1-6.

8. A pharmaceutical composition comprising a compound according to any of claims 1 to 7, or a pharmaceutically acceptable derivative thereof, in admixture with one or more physiologically acceptable carriers or excipients.

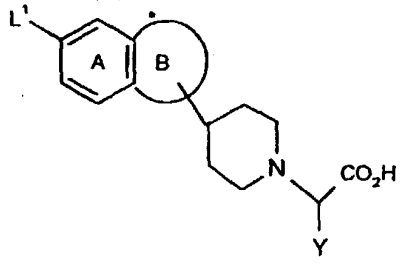
9. A compound according to any of claims 1 to 7 or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

10. Use of a compound according to any of claims 1 to 7 or a pharmaceutically acceptable derivative thereof in the manufacture of a therapeutic agent for the treatment of thrombotic disorders.

11. A method of treating a human or animal subject suffering from a condition which is mediated through the Glycoprotein complex GpIIb/IIIa or other integrin receptor which comprises administering to said subject an effective amount of a compound according to any of claims 1 to 7 or a pharmaceutically acceptable derivative thereof.

12. A method according to claim 11 wherein the condition is a thrombotic disorder.

13. A process for the preparation of a compound as defined in any one of claims 1 to 7, which comprises:
(i) according to a first process (A), compounds of formula (I) may be prepared by coupling a compound of formula (II)



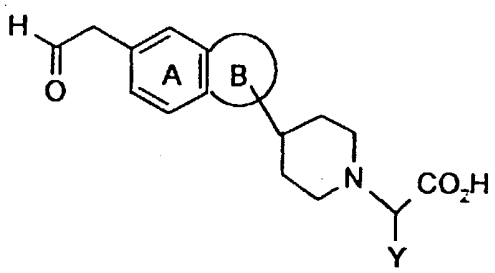
(II)

or a protected derivative thereof wherein L^1 represents a leaving group, for example, chloro, bromo or iodo, or a $-OSO_2CF_3$ group, with the alkene or alkyne of formula (III)

(III)

or a protected derivative thereof wherein:
L^1 is a leaving group, for example halo, or $-OSO_2CF_3$; ring system AB and Y are as defined above; and Z is piperidinyl or quinuclidinyl.

(ii) a further process (B), compounds of formula (I) wherein Z is piperazinyl may be prepared by reductive alkylation of a compound of formula (IV)

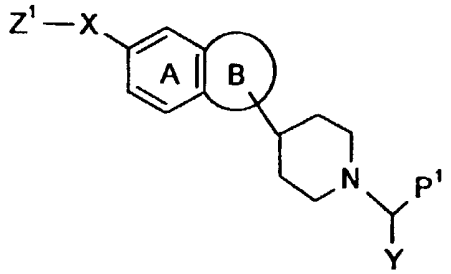


(IV)

or a protected derivative thereof, with piperazine wherein ring system AB and Y are as defined above, with piperazine;

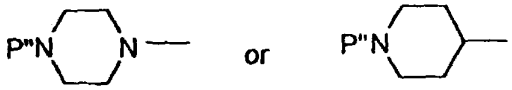
(iii) another process (C) compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) or protected derivatives thereof as precursors.

(iv) another process (D) for preparing compounds of formula (I) thus comprises deprotecting a compound of formula (V)



(V)

wherein Z^1 is quinuclidinyl,



ring system AB, X, and Y are as defined for formula (I); and

P' is a carboxyl group or a protected carboxyl group and P" is hydrogen or an amino protecting group, provided that when P' is a carboxyl group, P" is not hydrogen, and when Z^1 is quinuclidinyl P' is a protected carboxyl group.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 97/03194

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/14 A61K31/415 A61K31/41 A61K31/445 C07D413/14
C07D453/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 22303 A (GLAXO GROUP LTD ;MIDDLEMISS DAVID (GB); JUDKINS BRIAN DAVID (GB);) 11 November 1993 see the whole document ---	1-13
A	EP 0 542 363 A (GLAXO GROUP LTD) 19 May 1993 see the whole document ---	1-13
A	EP 0 635 492 A (LILLY CO ELI) 25 January 1995 see the whole document ---	1-13
A	EP 0 525 629 A (THOMAE GMBH DR K) 3 February 1993 see the whole document -----	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 1997	08. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Im ational application No.
PCT/EP 97/03194

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 11 and 12
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/EP 97/03194

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